ABSORB Bioresorbable Vascular Scaffold (BVS) for the Treatment of Coronary Artery Disease in Clinical Practice

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ABSORB Bioresorbeerbare Vasculaire Scaffold (BVS) voor de Behandeling van Coronairlijden in de Klinische Praktijk

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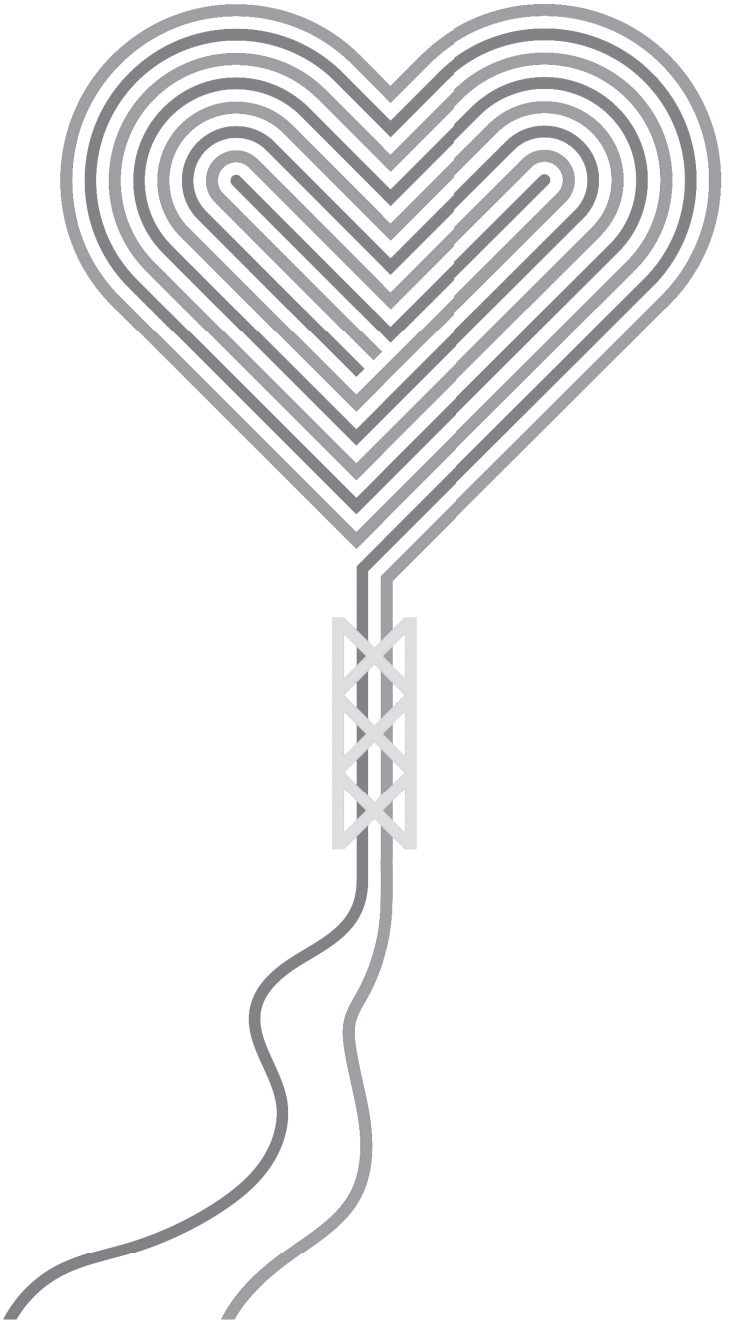
ABBREVIATIONS AND ACRONYMS

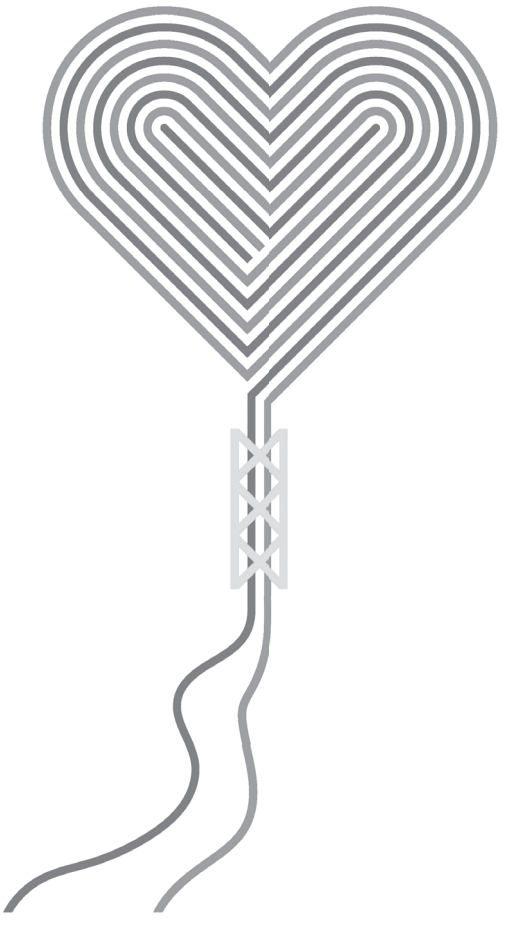
ACS	Acute coronary syndrome
AS	Area stenosis
Bif	Bifurcation
BMS	Bare metal stent
BRS	Bioresorbable scaffold
BVS	Bioresorbable vascular scaffold
CABG	Coronary artery bypass graft
Calc	Calcified
CAD	Coronary artery disease
CAG	Coronary angiogram
CTA	Computed tomography angiography
CTO	Chronic total occlusion
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DM	Diabetes mellitus
DS	Diameter stenosis
Dmax	Maximum diameter
Dmin	Minimum diameter
DOCE	Device oriented composite endpoint
ECG	Electrocardiogram
IVUS	Intravascular ultrasound
LAD	Left anterior descending coronary artery
LCX	Left circumflex coronary artery
LM	Left main
M	Month
MACE	Major adverse cardiac events
MI	Myocardial infarction
MLA	Minimal lumen area
MLD	Minimal lumen diameter
MSCT	Multislice computed tomography
NOAC	New oral anticoagulans
Non-TVR	Non-target vessel revascularization
NSTEMI	Nom ST-elevation myocardial infarction
OAC	Oral anticoagulans
OCT	Optimal Coherence Tomography
POCE	Patient oriented composite endpoint

PCI	Percutaneous coronary intervention
PLLA	Poly L- lactide
PT	Per treatment
QCA	Quantitative coronary analysis
RCA	Right coronary artery
RCT	Randomized controlled trail
RVA	Reference vessel area
RVD	Reference vessel diameter
SAP	Stable angina pectoris
ScT	Scaffold thrombosis
ST	Stent thrombosis
STEMI	ST-elevation myocardial infarction
TLF	Target lesion failure
TLR	Target lesion revascularization
TVR	Target vessel revascularization
UA	Unstable angina
VLScT	Very late scaffold thrombosis
VLST	Very late stent thrombosis



Introduction

General Introduction



Cardiovascular diseases (CVD), with coronary artery disease (CAD) being the most common type, are the leading cause of death globally. After numerous experiments on animals[1], coronary bypass grafting (CABG) was developed as treatment option for stenosed or completely occluded coronary. A German surgeon named Robert Goetz performed a CABG (IMA to LAD) on a human in a New York hospital in 1960, using a non-suture technique. The first suture technique based CABG procedure took place in 1964 by the Russian Vasilli Kolesov. Unfortunately, rate of mortality was high in these days, yet technology accelerated and improvements were made, which reduced the one-year mortality rate to approximately 3%. [2]

Andreas Gruentzig performed his first successful coronary angioplasty in 1977.[3] However, still in these early days many patients died or needed surgery the same day. Since then, numerous important developments have taken place within the field of interventional cardiology with a subsequent decrease in event rates. From the mid-eighties, the use of bare metal stents (BMS) reduced the high rate of acute recoil seen with classical angioplasty [4] but they went along with the frequent (up to 25%) occurrence of in-stent restenosis (ISR) within the first year after implant due to neointimal hyperplasia. [5] This phenomenon was contested by the introduction of metallic drug-eluting coronary stent (DES) in 1999 which subsequently, reduced the 1- and 2-year rates of restenosis and repeated revascularizations below 10% and soon, they became the gold standard for the treatment of CAD. However, DES were not devoid of limitations such as chronic inflammation, neoatherosclerosis, stent fracture, incomplete endothelization, loss of normal vessel geometry and vasomotion. Re-intervention rate using DES beyond 1 year post-implant, is on average 1 - 2% per year. [6, 7]

The mean age of patients treated with PCI is approximately 65 years. While treatment of ischemic heart disease improves and patients become older, the PCI population has quite some years to live after their first stent implant and the long-term risk of adverse events can be up to 20%. Therefore, new technologies have to be developed with the aim of improving outcomes beyond one year and envision 10 to 20 year durability of PCI. As mechanical support is most important to prevent acute recoil and preserving the lumen during the subsequent vascular healing process in the next three months, a temporary supportive device should be sufficient. This would eliminate the late response to the permanent metallic devices mentioned above.

Up to this moment, five bioresorbable scaffolds (BRS) received "Conformité Européene" (CE) mark: 1) the DESolve novolimus-eluting bioresorbable coronary scaffold system (Elixir Medical Corporation, Sunnyvale, California, USA), made of poly-L-lactic acid; [8] ; 2) ART Pure (Terumo Corporation, Tokio, Japan and Arterial Remodeling Technologies S.A. [ART], Noisy le Roi, France), a scaffold made of poly-D, L-lactic acid without any drug-elution; 3) the Magmaris scaffold (previously known as DREAMS, Biotronik AG, Bülach, Switzerland), a sirolimus-eluting and magnesium based scaffold. [9]; 4) Fantom (REVA

Medical, San Diego, California, USA), a sirolimus-eluting poly-tyrosine–derived polycarbonate scaffold. [10] 5) the everolimus-eluting Absorb bioresorbable vascular scaffold (BVS, Abbott Vascular, Santa Clara, California, USA), made of poly-L-lactide. Hypothesized advantages of the BVS over DES are late lumen enlargement, restored vasomotion, no interference with non-invasive imaging and complete resorption in approximately three years, leaving nothing behind. [11, 12]

The first iteration of the BVS (1.0) was tested in the ABSORB Cohort A in 2006. This study included only low-risk patients with simple lesions, with late lumen loss (LLL) as primary endpoint. [13] A second iteration of the device was developed with improvement in mechanical integrity and was tested in the ABSORB cohort B trial, revealing good results, with LLL of 0.19±0.18 mm at six months. Multiple randomized controlled trials (RCTs), mainly designed for regulatory approval in different countries which compare BVS with the best-in-class everolimus DES (Xience, Abbott Vascular, Santa Clara, California, USA), reported comparable results on the short-term (one year). [14-17] However, complex patients (acute myocardial infarction) and lesions (bifurcation, heavy calcification, chronic total inclusion [CTO]) were excluded. Because of the limited in- and exclusion criteria used in RCTs, patients included in registries are more representative of usual practise. Therefore, registry-based results are important and have a higher generalizability.

At the Absorb BVS's clinical introduction in September 2012, the Erasmus Medical Centre started two prospective, single-arm, investigator-initiated registries as a structured program, aiming at hospital quality control and an increase in knowledge to share with the interventional cardiology community through scientific publications. Up to this day, there is still a lack of data concerning the implementation of this new technology in 'real-world' patients, consisting of more complex subsets such as ACS patients, calcified and bifurcation lesions and with a longer duration of follow-up.

Scope of this thesis

The aim of this thesis is to investigate the early and mid-term performance of the Absorb BVS in more complex lesions and higher-risk patients, when treated in a diverse clinical practice.

Also, the purpose is to identify potential factors that could influence these outcomes to optimize patient and lesion selection, procedural strategies and post-procedural pharmaceutical treatment. Lastly, more information is necessary regarding the mechanisms of scaffold failure (both scaffold thrombosis and restenosis) and to develop this treatment further and treatment options are provided.

The early outcomes of this new device in will be investigated in Part I, using different quantitative techniques in different clinical scenarios. We will use early proven surrogate endpoints and look at short-term outcomes.

Part II will examine the mid-term outcomes in relation to complex lesion and patient subtypes and clinical presentations to identify predictors of potential unfavourable

results. This was done in a more general population and in specific higher-risk groups such ACS patients, calcified and bifurcation lesions.

Part III will report on late events, occurring during the resorption phase. It will focus on scaffold thrombosis and restenosis and concerns results from cases with poor outcome. Also, we will provide some suggestions for how to handle these.

In the final section (Discussion), observations from this research will be discussed while integrating these with the current international literature to an updated statement on the use of this first-generation bioresorbable vascular scaffold and directions for improvement in outcome.

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Chapter 1

Current status of clinically available bioresorbable scaffolds in percutaneous coronary interventions

CM Felix, BRC Everaert, R Diletti, NM van Mieghem, J Daemen, M Valgimigli, PP de Jaegere, F Zijlstra, ES Regar, C Simsek, Y Onuma, RJM van Geuns

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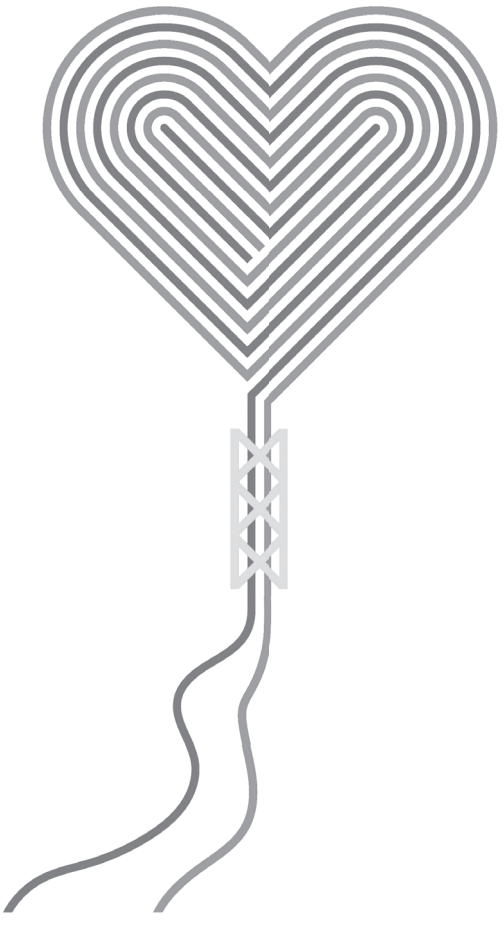

ABSTRACT

Drug eluting stents are widely used as first choice devices in percutaneous coronary interventions. However, certain concerns are associated with the use of drug-eluting stents (DES), i.e. delayed arterial healing with a subsequent risk of neo-atherosclerosis, late stent thrombosis and hypersensitivity reactions to the DES polymer. Bioresorbable vascular scaffolds (BVS) are the next step in percutaneous coronary interventions introducing the concept of supporting the natural healing process following initial intervention without leaving any foreign body materials resulting in late adverse events. The first generation devices have shown encouraging results in multiple studies of selected patients up to the point of full bioresorption supporting the introduction in regular patient care. During its introduction in daily clinical practice outside the previous selected patient groups, a careful approach should be followed in which outcome is continuously monitored.

INTRODUCTION

Drug-eluting stents (DES) are widely used as devices of first choice in percutaneous coronary interventions (PCI). However, certain concerns are associated with the use of DES, i.e. delayed arterial healing with a subsequent risk of neo-atherosclerosis, late stent thrombosis and hypersensitivity reactions to the DES polymer [1].

Furthermore, from a more general physiological point of view, a vessel that is indefinitely caged in a metal scaffold is not desirable both on short and long term, because of the risk of impaired endothelial function, the reduced potential for vessel remodelling, interference with the normal arterial healing process and the risk of occlusion of covered side-branches by neointima hyperplasia. Also, interference with non-invasive imaging (cardiac computed tomography or magnetic resonance imaging) during patient follow-up and possible impairment of future treatment options (re-percutaneous coronary interventions or coronary artery bypass surgery) are drawbacks of metallic stents [2]. Therefore, a stent type made of a bioresorbable material could provide the desirable transient vessel support without compromising the restoration of normal vessel biology, vessel imaging or treatment options in the long run. Furthermore, the need for long-term dual anti-platelet therapy (DAPT) could potentially be reduced.

The Igaki-Tamai stent was the first-in-man fully biodegradable coronary stent made of poly-L-lactic acid (PLLA). However, this stent did not possess any active anti-proliferative drug coating and this resulted in an unacceptably high early target vessel revascularisation rate. On the other hand, late invasive follow-up confirmed the fully bioresorption process and coverage of complex atherosclerotic lesions with a stable layer of neo-media . From September 1998 until April 2000, 50 patients were treated. Data of 10 year follow-up showed highly first year target vessel failure (TVF) with acceptable rates of major adverse cardiac events (MACE) during the late follow [3].

The Absorb Bioresorbable Vascular Scaffold (BVS, Abbott Vascular, Santa Clara, CA) consists of a poly L-lactide (PLLA) bioresorbable scaffold with poly D, L-lactide bioresorbable (PDLLA) coating that releases the anti-proliferative drug everolimus. The long chains of PLLA and PDLLA are degraded via hydrolysis of the ester bonds and the resulting lactate and its oligomers are metabolized by the pyruvate and Krebs energy cycles. Two adjacent radio-opaque platinum markers are located at both Absorb edges to allow long term visualisation. The strut thickness is approximately 150 µm.

There is suggested that patients treated with a BVS need more aggressive anti-platelet therapy because of these thicker struts. Prasugrel, a third-generation thienopyridine prodrug, induces platelet inhibition more consistently and to a greater extent than clopidogrel which resulted in less stent thrombosis, urgent target vessel revascularisation and myocardial infarct a the costs of a small increase in major bleedings in the randomized controlled PLATO study [4]. The Rijnmond Collective Cardiology Research (CCR)

registry is a prospective, observational study that will assess the adaption of Prasugrel into routine clinical practice and in the nearby future will deliver real-world numbers about reducing ischemic events on one hand and the increased risk of bleeding on the other hand [5]. If safety is confirmed in this routine clinical practice prasugrel might be the preferred treatment for patients treated with BVS.

The Absorb Bioresorbable Vascular Scaffold was the first fully bioresorbable scaffold that received a CE-mark. A comparable PLLA based scaffold coated with myolimus has completed its first-in-man study with encouraging results and also obtained CE-mark [6]. With its current limited scientific evidence of efficacy this review will concentrate on the only widely available BVS, the Absorb scaffold.

The beginning of BVS: ABSORB Cohort A and B

ABSORB Cohort A was the first-in-man trial to investigate the safety and feasibility of the everolimus-eluting bioresorbable vascular scaffold (BVS). In this prospective, multi-center, single arm, open-label trial thirty patients with stable, unstable or silent ischemia were enrolled from March until July 2006. Coronary lesions had to be single and *de novo* in a native coronary artery with a stenosis of > 50% and with a TIMI flow grade > 1.

Major exclusion criteria were ST-elevation myocardial infarction (STEMI) patients, patients presenting with unstable arrhythmias or those with a ventricular ejection fraction < 30%. Significant stenosis in the left main coronary artery, lesions involving a side branch > 2 mm in diameter and lesions with the presence of thrombus or more than one clinically significant stenosis in the target vessel were excluded.

The clinical endpoints were assessed at 30 days, 6 and 9 months and 1, 2, 3, 4 and 5 years and were excellent. Except from one non-Q wave myocardial infarction no other major adverse cardiac events were noted up to 2 years (defined as cardiac death, myocardial infarction (MI) and ischemia-driven target lesion revascularization (TLR)).

After 2 years, invasive coronary imaging studies showed that the BVS were largely absorbed and had been incorporated into the vessel wall. The remaining strut parts were apposed and late lumen enlargement could be demonstrated. Vasomotion and endothelial function were evaluated after intracoronary injection of methergin (a vasoconstrictor) and acetylcholine (an endothelium-dependent vasodilatator). This confirmed restoration of normal endothelium-dependent vessel wall function after degradation of the vascular scaffold [7]. (Figure 1)

A 5-year clinical follow up was obtained in twenty-seven patients (one patient withdrew consent and two patients died of a non-cardiac cause). Major adverse cardiac event rate at 5-year follow-up was low (3.4%). No scaffold thrombosis was reported [8]. In ABSORB Cohort A the first generation device was used. Tanimoto et al. described that acute stent recoil was slightly but insignificantly larger when compared to that of the everolimus-eluting stent (EES) (6.9% vs 4.3%) [9]. This first generation BVS showed a late

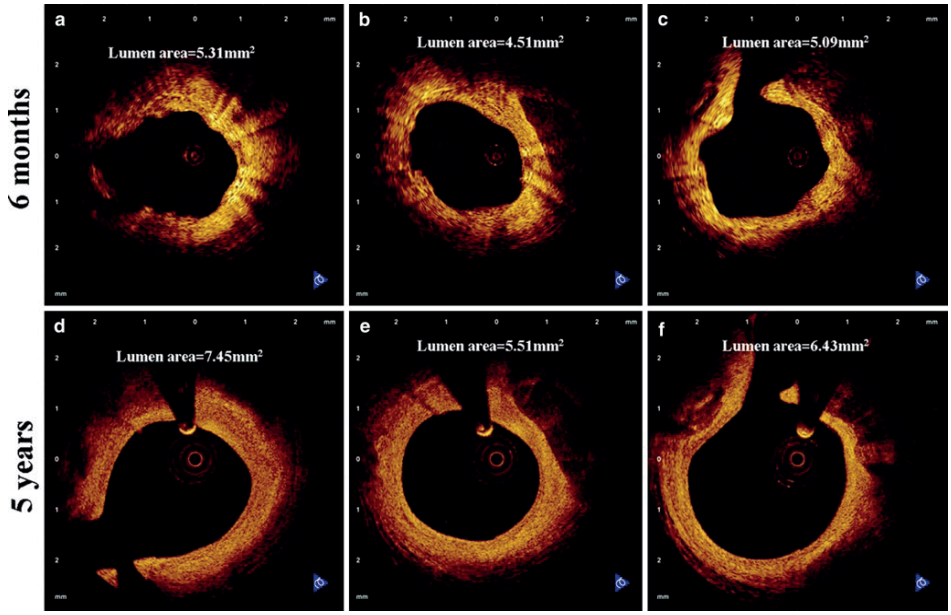

Figure 1 Optical coherence tomography images of coronary arteries from matched sites at 6 months (A-C) and 5 years (D-F) after BVS implantation
(Adapted from A. Karanasos et al. (33))

lumen loss of 0.44 mm, probably due to device shrinkage. To overcome the potential issue of acute scaffold recoil, a second generation BVS with a modified scaffold design was tested in the ABSORB Cohort B trial. This revised scaffold was developed to provide a greater vessel wall support, a more consistent drug delivery and device storage at room temperature.

The ABSORB Cohort B trial had a prospective, multicenter, single arm, open-label design. Hundred and one patients were included and subdivided into two groups according to the invasive imaging protocol. The first group (B1, n = 56) underwent angiography at 6 and 24 months and the second group (B2, n = 45) received follow-up angiography at 12 and 36 months. Also, during angiography, the implanted scaffolds were additionally investigated with intravascular ultrasound (IVUS) and optical coherence tomography (OCT). In ABSORB Cohort B, patients with a maximum of 2 de novo coronary artery lesions were included (maximum lesion diameter and length of 3.0 mm and 14 mm respectively, for a scaffold size of 3.0 x 18 mm). The other in- and exclusion criteria did not differ from the ABSORB Cohort A trial. At 3 year follow up there had been no cases of cardiac death or scaffold thrombosis, three cases of myocardial infarction (all non-Q-wave), and seven ischemia-driven target lesion revascularization with a major cardiac adverse event rate of 10%. No scaffold thrombosis was evident during follow-up [10].

Imaging with intravascular ultrasound demonstrated late lumen enlargement of the scaffolded lesions in the ABSORB cohort A and B patients. This observation could represent a paradigm shift from late lumen loss to late lumen gain when applying BVS

Also, results on restoration of vasomotor function were reported for the ABSORB A and B Cohorts. These data suggest a progressive recovery of normal vascular function in the scaffolded segments during the resorption process [11].

Recently Karanasos et al reported about the long-term vascular healing response of 8 patients from the ABSORB Cohort A. 5 years after BVS implantation patients underwent invasive follow-up with optical coherence tomography , revealing late luminal enlargement, complete strut bioresorption and development of a 'sealing layer' covering underlying thrombogenic plaque components [12].

In brief, the ABSORB Cohort A and Cohort B trial included only non-complex lesions with low-risk patients. Placement of BVS proved to be feasible and safe, with major cardiac adverse events and stent thrombosis rate similar to Xience V. Based on the clinical safety demonstrated in the first studies (ABSORB Cohort A and B), the everolimus-eluting BVS acquired a CE-mark in Europe and has since become commercially available. However, to further expand the indication for BVS use in more complex coronary lesions and acute coronary syndrome patients, the BVS Expand, ABSORB Extend and ABSORB II and BVS STEMI first study, respectively, were initiated.

Extend clinical evaluation of BVS

To explore the performance of BVS in a larger group of patients with different operators, the ABSORB Extend study was initiated in more than 100 non-US sites worldwide. This continued access, non-randomized, prospective, single arm clinical trial was started in January 2011 and intended to include more than 800 patients with up to 2 *de novo* lesions in different epicardial vessels. The range of scaffold diameters and sizes was extended (2.5, 3.0 and 3,5 mm in diameter and 12, 18 and 28 mm in scaffold length, respectively) to allow the treatment of a broader range of coronary lesions (≤ 28 mm in length and reference vessel diameter of 2.0-3.8 mm (as assessed by on-line QCA or intravascular ultrasound)). One stent overlap was allowed for lesions of more than 22 and less than 28 mm. Target lesions located in the left main coronary artery, arterial or saphenous vein grafts, in-stent restenosis, lesions previously treated with brachytherapy, chronic total occlusions (CTO, TIMI 0 prior to wire crossing), bifurcation lesions with side branches ≥ 2 mm in diameter, ostial lesion of > 40% stenosis or a side branch requiring pre-dilatation were excluded from the study. Also lesions with excessive calcification, high tortuosity or visible thrombus were excluded.

Recently, an interim analysis on the twelve-month clinical outcome of the 512 first BVS implanted patients demonstrated a favourable clinical outcome and safety profile (Table 1). Cardiovascular death, ischemia-driven major adverse cardiac events and

Table 1. Overview of currently reported BVS studies and registries.

	EXTEND	ASSURE	ABSORB FIRST	EXPAND	AMC	Milan	GHOST-EU	BVS STEMI first	Mainz ACS	Polar ACS	Prague-19
N	512	183	800	200	135	92	1189	49	150	100	76
Sites	56	6	95	1	1	2	10	1	1	Multi	2
Period	1/10-12/12	4/12-3/13	1/13-3/14	9/12-10/13	8/12-8/13	5/12-8/13	11/11-1/14	11/12-4/13	5/12-6/13	?-10/13	12/12-4/14
Acute coronary syndrome	0%	21.3%	38%	60.4%	48.8%	10.9%	47.4%	100% (all STEMI)	100%	100%	100% (all STEMI)
Single vessel PCI	93%	-	90.7%	61.5%	81.1%	-	-	100%	-	100%	-
Lesions/patient	1.1	1.1	1.2	1.4	1.2	1.5	1.2	1.0	1.2	1.0	1.2
Lesion length	11.9 mm	15 mm	18.3 mm	25.4 mm	-	36.5 mm	19.4 mm	26.4 mm	19.4 mm	-	23.2 mm
Calcification (moderate/ severe)	15%	15.7%	20.4%	45.8%	11.3%	20.4%	-	-	-	-	-
B2	41%	43.4%	23.1%	24.4%	42.1%	83.9% (B2+C)	23.6%	-	-	-	-
C	2%	21.2%	23.6%	16.7%	25.2%		27.6%	-	-	-	-
Device success	98.6%	-	98.9%	98.2%	96%	-	99.7%	97.9%	-	100%	96.2%
Target lesion revascularization	1.8% at 1 year	2.8% at 1 year	-	2.2% at 6 months	5.0% at 6 months	3.3% at 6 months	2.5% at 6 months	0% at 30 days	2.0% at 30 days	0% at 1 year	1.3% (average of 6 months FU)
Target vessel revascularization	-	-	-	2.2% at 6 months	6.6% at 6 months	3.3% at 6 months	4.0% at 6 months	0% at 30 days	-	1.1% at 1 year	-
Definite stent thrombosis	0.8% at 1 year	0% at 1 year	0.3% at 30 days	2.2% at 6 months	3.2% at 6 months	0% at 6 months	1.7% at 6 months	0% at 30 days	2.0% at 30 days	1.1% at 1 year	1.3% (average of 6 months FU)
Major Adverse Cardiac Events	4.3% at 1 year	5% at 1 year	-	3.3% at 6 months	-	3.3% at 6 months	-	2.6% at 30 days	6.6% at 30 days	3% in-hospital	2.6% (average of 6 months FU)

target vessel failure occurred in 0.4, 4.3 and 4.9% of patients respectively. The incidence of scaffold thrombosis was low (0.8%) [13]. Propensity matched clinical outcomes at one year showed identical cardiovascular death, hierarchical major adverse cardiac event and stent thrombosis rates for BVS compared to second generation DES (Xience V) (0.3 vs. 0.6%, 5.2 vs. 5.5% and 0.5 vs 0.5%, respectively) [14] . Interestingly, in a propensity score analysis comparison between Absorb Cohort B/ Extend patients and Xience V patients from Spirit Cohorts, target vessel failure rates were significantly lower in BVS compared to DES (5.5 vs. 8.6%, respectively, p = 0.04). A 2-year follow-up propensity matched analysis confirmed the non-inferiority of BVS compared to Xience V [15].

Interestingly, the result from a propensity matched analysis of 250 patients, comparing patients implanted with BVS to patients implanted with Xience V in the SPIRIT IV trial, showed a decrease in angina pectoris reported by the sites through adverse event reporting at one year (16.0 vs 28.1%, respectively) [16]. This difference was highly significant and probably accounts for the lower target vessel failure rate in the BVS group. Also, the percentage of angina diagnosed through adverse event reporting was notably lower with BVS than that reported in previous large interventional trials (FREEDOM (sirolimus-eluting stent/paclitaxel-eluting stent): 21%; SYNTAX (paclitaxel-eluting stent): 28%; COURAGE (bare metal stent: 34%) (16). Further follow-up is needed to confirm this observation on the potential reduction of post-percutaneous coronary intervention angina. If confirmed, repeat angiography with or without additional coronary intervention would be significantly reduced. This could greatly impact on patient quality of life and additionally reduce health care costs.

The ABSORB II study started in November 2011 as the first randomized (2:1), prospective, single-blinded, multicenter trial, in which patients were assigned to the ABSORB BVS or a second generation everolimus-eluting coronary stent (Xience Prime). A total of 501 patients were randomized across forty European sites and in New Zealand. Patients with stable or unstable angina, silent ischemia and with up to 2 *de novo* lesions in different epicardial vessels with a maximal lesion length of 48 mm were enrolled. Major exclusion criteria were STEMI, left ventricular ejection fraction < 30%, unstable arrhythmias, left main disease, chronic total occlusions and severely calcified or tortuous lesions. Patients will be followed for five years, with an invasive evaluation by angiography, intravascular ultrasound, optical coherence tomography, and vasomotion testing at final follow-up for superiority [17]. First one year interim analysis showed non-inferiority between BVS and DES on major adverse cardiac events which is essential to achieve the superiority endpoint [18].

BVS in more complex coronary lesions in every day patients.

In September 2012, at the Erasmus MC, the Expand registry was initiated to evaluate the long term safety and performance of the BVS in routine clinical practice. In this monocenter, prospective, observational registry, patients presenting with non ST-

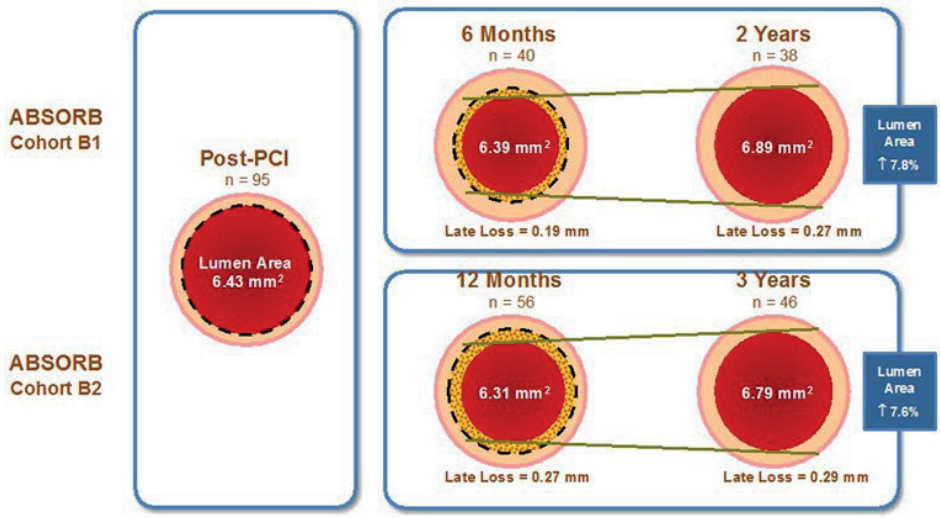

Figure 2 Evolution of the IVUS-measured mean lumen area in coronary arteries treated with BVS in ABSORB Cohort B1 and B2

elevation myocardial infarction (NSTEMI), stable or unstable angina or silent ischemia in combination with a *de novo* stenotic lesion in a native, previously untreated, coronary artery were included. A reference vessel diameter up to 4 mm and a longer lesion length (> 32 mm) was allowed, as was a higher degree of calcification and bifurcation lesions. Major exclusion criteria were previous coronary artery bypass graft or metallic stent in the target vessel, cardiogenic shock, STEMI, bifurcation lesions requiring kissing balloon post-dilatation, allergy or contra-indications to dual antiplatelet therapy. In the first 200 patients, on average 1.9 scaffolds were implanted per patient, with stent overlap in 32% of patients. Mean lesion length was 25.4±13.5 mm. 41.1% of lesions were scored as B2 or C lesions, 5.8% were chronic total occlusions and in 29.1% a bifurcation was included. 38.5% of patients had multi-vessel disease. The procedural success rate of BVS implantation was 98.2%, with a radial approach in 76.6% and lesion preparation in 91.9% of lesions (275 in total). The six months results were excellent with a mortality of 2%, a definite scaffold thrombosis of 2.2% and no other target lesion revascularization within this period. Final rate of major adverse cardiac events at 6 months was 3.3% (Table 1) [19].

Recently, the 6 month outcome data of the Italian all-comer patient GHOST-EU registry, including 1189 patients with moderate to high complex lesion and/or patient characteristics, were reported, showing acceptable rates of cardiovascular death (1.0%), target vessel myocardial infarction (2.0%) and of target lesion failure (4.4%) [20]. Definite scaffold thrombosis rates were 1.7% at 6 months. Also, the Academic Medical Centre (AMC) single arm first experience, including a high number of complex patients, showed a somewhat higher major adverse cardiac events rate at this time point, especially re-

lated to scaffold thrombosis. The investigators claim that this was due to a learning curve where major changes were made with regard to lesion preparation and post-dilatation to achieve full scaffold expansion and avoiding underexpansion as observed in the first scaffold thrombosis cases [21]. Conversely, a propensity matched analysis from the single center San Raffaele Scientific Institute BVS registry (Milan, Italy), comparing BVS (n = 92) with Xience V (n = 92) in complex lesions (83.9% B2 or C lesions, 45.2% bifurcations), did reveal similar early outcomes of BVS to second generation DES and no evidence for increased scaffold thrombosis rates [22].

Other registries mainly including less complex lesions have provided good data on BVS safety and performance in true clinical experience. The German multi-center ASSURE registry showed low rates of cardiovascular death, myocardial infarction and target lesion revascularization (0.5, 1.6 and 2.8%, respectively) at twelve months after implantation (n = 183). No cases of scaffold thrombosis were observed [23]. Lastly, the ongoing multi-center ABSORB FIRST study was designed to enrol a high number of moderately complex 'real world' patients. An interim analysis of the results from the first 800 patients at 30 days of follow-up demonstrated excellent device success rates (98.9%), no cases of cardiovascular death and a low risk of definite or probable scaffold thrombosis (0.3%) [24].

BVS in ACS and STEMI patients: what do we know?

Immediately after clinical availability several institutions started treatment of more complex lesions with strict follow-up in several registries. We excluded STEMI patients as large amount of thrombus is usually present which might result in malapposition if resolved in time. In the first registries a high number of NSTEMI patients where included of which a significant number early angiography demonstrated full vessel occlusion, an observation made by others [25]. After thrombus aspiration BVS implantation was performed in a similar fashion as non-ACS patients and OCT controlled showed excellent apposition. This opened the door for BVS in STEMI patients.

In 2013, Wiebe and co-workers presented a first report on the short-term outcome of STEMI patients treated with an everolimus-eluting bioresorbable scaffold. Twenty-five patients with thirty-one lesions were included with a procedural success rate of 97% and major adverse cardiac event rate of 8.3% during a mean follow-up period of 137 days [26].

Recently, our group reported the 30-day clinical outcome of the BVS STEMI First Study. In this prospective, single-arm, monocenter safety and feasibility study 49 STEMI patients were treated with a BVS (direct stenting in 32.7% and pre-dilatation in 67.3%). The procedural success rate of BVS implantation was 97.9%. TIMI-flow III was obtained in 91.7% of patients after BVS implantation. At 30 days, the major adverse cardiac event rate was 2.6% (one patient with a non Q-wave myocardial infarction in a non-target vessel). Target lesion failure (composite of cardiac death, target-vessel myocardial infarction

or ischemia driven target lesion revascularization) did not occur and there were no cases of scaffold thrombosis [27].

Additionally, in the prospective Prague 19 trial, BVS were implanted in consecutive STEMI patients from December 2012 until August 2013. The authors recently reported on forty-one patients who received a BVS compared to a control group who were implanted with a drug eluting or bare metal stent (n = 57) [28]. BVS device success rate was 98%. There were two events in the BVS group: one early (day 13) scaffold thrombosis after stopping aspirin and ticagrelor for which the patient underwent re-PCI and one non-target vessel myocardial infarction after a staged procedure with a DES. Four events (one cardiac death, two patients with unstable angina due to stent thrombosis and one myocardial infarction in a non-target vessel) were witnessed in the control group (95% for BVS and 93% for the control group, p = 0.674).

Recently, an update of the Prague-19 study, comprising seventy-six STEMI patients implanted with BVS was presented during EuroPCR 2014, showing a target lesion revascularization of 1.3%, and a stent thrombosis and major adverse cardiac event rate of 1.3% and 2.6%, respectively, with an average follow-up of about 6 months [29]

Concerning acute coronary syndromes, Gori et al reported the short-term results in hundred and fifty consecutive patients (unstable angina 16%, NSTEMI 40%, STEMI 44%), treated with in total 194 BVS between May 2012 and July 2013. These patients were compared with 103 consecutive control patients who received a DES (XIENCE Prime). Major adverse cardiac event rates at thirty days and six months were similar between both groups. Scaffold thrombosis occurred in three BVS patients and two DES patients within the first month [30].

Also the POLAR ACS study (100 patients; unstable angina 46%, NSTEMI 38%, STEMI 16%), reported excellent device success rate (100%) with limited (3.0%) in-hospital major adverse cardiac event rate (due to two peri-procedural myocardial infarctions and one non-target vessel revascularization) [31].

Overall, the first trials although still on a small number of patients, suggest that implantation of BVS in STEMI patients is feasible and safe, with early outcomes comparable to drug-eluting metal stents. However, these preliminary data need to be confirmed in future larger randomized controlled trials.

GENERAL CONCLUSION

Bioresorbable coronary artery scaffolds are the next step in percutaneous coronary intervention introducing the concept of the natural healing following percutaneous coronary intervention without leaving foreign body material in situ. The first generation devices have shown encouraging results in selected patient studies up to the point of

fully bioresorption supporting the introduction in regular patient care. During their introduction in daily clinical practice outside the previously selected patient groups a careful approach should be followed where outcome is continuously monitored.

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Chapter 2

Appropriate use of bioresorbable vascular scaffolds in percutaneous coronary interventions: a recommendation from experienced users

A position statement on the use of bioresorbable vascular scaffolds in the Netherlands

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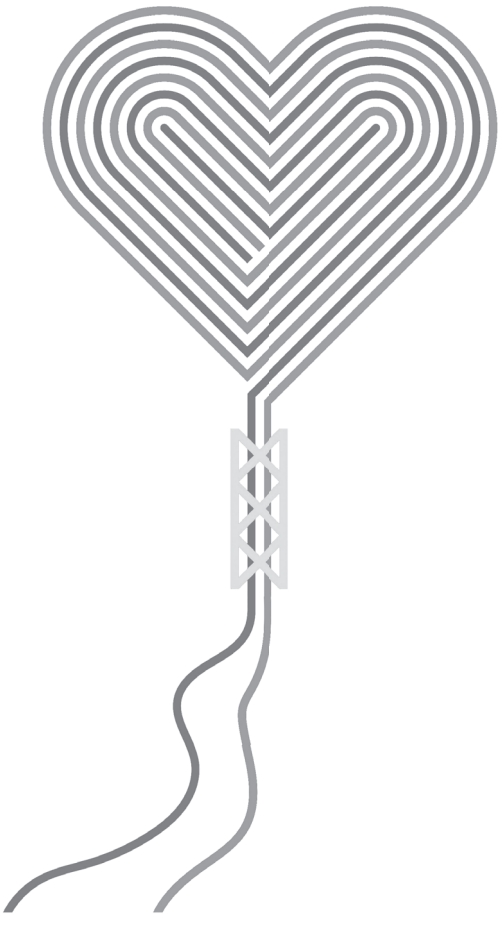

INTRODUCTION

Percutaneous coronary interventions (PCI) have become a reliable revascularization option to treat ischemic coronary artery disease (CAD) [1]. Drug eluting stents (DES) are widely used as first choice devices in many procedures due to their established good medium to long term outcomes [2]. These permanent implants however, do not have any residual function after vascular healing following the PCI. Beyond this initial healing period, metallic stents may induce new problems, resulting in an average rate of 2% reinterventions per year [3]. To eliminate this potential late limitation of permanent metallic DES, bioresorbable coronary stents or 'Vascular Scaffolds' (BVS) have been developed. In a parallel publication in this journal an overview of the current clinical performance of these scaffolds is presented. As these scaffolds are currently CE-marked and commercially available in many countries and as clinical evidence is still limited, recommendations for their general usage are needed to allow for a successful clinical introduction.

Introduction of new technologies

Continuous technological innovation has contributed to the impressive improvement of medical care over the past decades. On the other hand, many new technologies failed to deliver on their promises and disappeared soon after introduction, such as coronary laser angioplasty and brachytherapy. Moreover, recently, several examples exist of new technologies that were introduced without appropriate recommendations and assessment. A recent example is the introduction of a metal-on-metal hip prosthesis, considered beneficial for younger patients, in which an unexpectedly high rate of device failure was present. Based on similar examples, the Dutch Society of Cardiology (NVVC) adopted policy documents for the introduction of new technologies [4]. Later, the Dutch Order of Medical Specialists in collaboration with 'Zorginstituut Nederland' composed a similar document for all medical specialists in the Netherlands [5]. Both documents provide important information on the introduction process for new devices. In these documents a preparation phase is described including a risk analysis and a multi-disciplinary co-operation before advising on device introduction. Furthermore, post-introduction outcome registration and reporting are essential to assess for any unexpected adverse events. Also, due to the substantial increase in health care costs when CAD patients have to undergo PCI and taking into account that the number of PCI has more than a doubled over the past 10 years in the Netherlands [6-7], the cost-effectiveness of any new PCI technology remains an important issue. Regarding the need of adjunctive imaging and supporting techniques for optimal BVS placement, the cost-effectiveness of treating CAD with BVS has yet to be determined in an all-comer patient population.

Lesion selection

Numerous reviews on the current status of bioresorbable vascular scaffolds (BVS) for PCI have been published. In this journal, we have updated these reviews with the latest data presented during the EuroPCR meeting from May 20th to 23rd 2014 in Paris. In short, the safety of BVS has once again been confirmed in a large group of patients for non-complex lesions up to 2 years after scaffold implantation after initial good results for 5 years in smaller groups [8-9]. Based on these results we think that the use of the Absorb BVS can be considered as 'appropriate' for lesions that were included in the initial ABSORB Cohort A and B trial and the ABSORB Extend registry. The details of these 'Absorb Extend-like lesions' are summarized in Table 1. The first randomized study (ABSORB II trial) on whether the Absorb BVS offers an advantage over DES is currently ongoing. The results of the physiologic study will be available in 2016. An interim analysis at one year of follow-up showed similar rates in a composite clinical endpoint based on death, myocardial infarction and coronary revascularization [10].

Table 1 BVS Extend-like lesions.

Absorb Extend-like lesions	Exclusion
'de novo' lesions	Left main
Diameter 2.3 - 3.8 mm	Arterial or venous grafts
Length max 28 mm	In-stent restenosis
One BVS scaffold overlap	Chronic total occlusion (CTO)
Maximum 2 lesions	Ostial lesions
Stable, unstable or silent ischemia	Bifurcation lesions with side branches ≥2 mm diameter
	Excessive calcification
	High tortuosity
	Visible thrombus
	(N)STEMI
	LVEF <30%

NSTEMI non-ST-elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction

For patients with more complex lesions, who were excluded from the initial BVS studies, some short term data have been reported during the last EuroPCR meeting. In addition, several medium sized trials (100-300 patients) with outcome data up to 12 months were also presented. Based on these data and the experience of the authors, the previous exclusion criteria for the Absorb BVS use currently seem outdated. However, as the follow-up period for these more complex lesions as well as patient numbers are still limited, the level of recommendation made cannot exceed 'probably appropriate'. With this limited evidence in mind, it is important for every operator and PCI center to keep a

registry of patients treated with BVS including data on patient outcomes as described in the NVVC guideline on the introduction of new technologies.

Within these real world registries the number of patients with true complex lesions, such as two scaffold bifurcations, heavily calcified lesions with rotablator lesion preparation and CTO is limited. For these complex lesions no recommendation can be given as the patient number is too small and the outcomes are still uncertain. Probably, the AIDA (Amsterdam Investigator-initiateD Absorb strategy All-comers) trial, a Dutch multicenter trial with over 2700 patients included will provide more insights into the use of BVS in these more complex lesions.

Furthermore, two special subsets of lesions should be mentioned: arterial or venous grafts and in-stent restenosis (ISR). For both, the current Absorb BVS label (de novo lesions in native vessels) does not apply and at this moment for these types of lesions the recommendation has to be off-label which should only be deviated from with a clear motivation.

Table 2 Lesion selection.

Appropriate	Absorb A/B and Extend-like lesions: 'de novo' lesions, max. length 28mm, one stent overlap, max. 2 lesions
Probably appropriate, early evidence	ACS patients, long lesions (>28 mm), calcified lesions with proper lesion preparation (diameter stenosis <40% after preparation), provisional bifurcation treatment (including fenestration into side branch)
Uncertain	Bifurcations requiring a two scaffold approach Chronic total occlusion with subintimal crossing Extensively calcified lesions where aggressive lesion preparation is necessary
Off-label	In-stent restenosis Arterial and venous grafts Vessels > 4.0 mm in diameter

ACS acute coronary syndrome

A final - technical - limitation is the overexpansion capabilities of the Absorb BVS that is currently restricted to 0.5 mm. As the largest commercially available Absorb BVS is 3.5 mm at nominal pressure, vessels with a diameter above 4.0 mm (quantitatively measured by QCA, IVUS or OCT) should not be targeted because of the greater risk of extensive malapposition.

PATIENT SELECTION

Every introduction of a new technology targets a specific subgroup of patients. With the introduction of DES with higher health-care costs, initially, only patients with a high risk of early restenosis (DM patients, long lesions and small vessels) were selected.

Solid clinical data and a price cut paved the way for DES use in the majority of patients undergoing PCI in the Netherlands. As bioresorbable therapy aims to improve patient outcomes after the first year of implantation, patient selection has to take into account other arguments. Although many classical predictors of early restenosis also apply for treatment failure beyond one year (j-Cypher Registry) i.e. diabetes mellitus (DM), renal failure, dialysis and long lesions, some factors are less important for long term TLR such as bifurcation lesions with side branch stenting [11]. It is important to make a differentiation between factors mainly affecting late TLR and those also impacting on patient long term (>5 year) survival.

It is therefore essential to appropriately select patients in which BVS may yield the highest beneficial effect on long time clinical outcome. The American NCDR registry recently provided valuable information for patient selection [12]. Although a relatively complex model was used, some major points have been identified. Patients above >80 years, patients with severe renal failure or on dialysis or patients who are in cardiogenic shock at the time of the procedure, have a limited live expectancy and therefore the overall potential long term benefit of BVS therapy is very limited. Other patient-related conditions, such as DM, body mass index (BMI) >40, left ventricular ejection fraction (LVEF) <40%, CVA, peripheral artery disease (PAD) and chronic obstructive pulmonary disease (COPD), have a negative impact on patient's life expectancy and should lower the upper age limit for patient selection. In table 3 we provide a simplistic model that can be used for patient selection.

Table 3 Patient specific criteria.

Optimal	Young patients or with good life expectancy (i.e. >5 years)	Age <70 years or age 70-80 with max 1 of PAD, COPD, CVA, renal failure, DM, BMI >40 or LVEF <40%
No potential benefit to be expected	Limited life expectancy (i.e. <1 or 2 years)	Cardiogenic shock, severe heart failure (EF <30%), dialysis

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *CVA* cerebrovascular accident, *DM* diabetes mellitus, *LVEF* left ventricular ejection fraction, *PAD* peripheral artery disease

Technical considerations for BVS implantation

Lesion preparation is especially important, as the current Absorb BVS strut thickness is higher (150 µ) than that of conventionally used DES. Also, before inflation, the initial scaffold diameter is quite large (1.4 mm) which is related to the specific scaffold-related folding characteristics of the Absorb BVS. Therefore, highly calcified or tortuous lesions or lesions with a high degree of angulation can be quite challenging for BVS implantation. However, with extensive lesion pre-dilatation using increasing balloon sizes, even highly calcified lesions can be successfully treated with BVS, although special care has to be paid to a good implantation technique. In summary, the 5 golden 'P's for BVS implan-

tation: Prepare the lesion, Properly size the vessel, Pay attention to the expansion limits of the BVS, Post-dilate the scaffold with a properly sized non-compliant balloon and pay attention to the DAPT compliance of the patient.

To avoid BVS malapposition, also taking into consideration the current limited sizes in scaffold diameter and length, correct scaffold sizing based on reliable assessment of vessel dimensions is a second important issue. Invasive imaging modalities, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), have been proven to be superior to angiography in providing accurate morphometry, including for estimating vessel diameter and lesion length. OCT is particularly suited to visualize the scaffold struts and their interaction with the vessel wall and can greatly improve the quality of BVS implantation [13]. Before implantation, OCT is indicated to predetermine lesion characteristics, such as lesion length and the amount of calcification, to estimate the optimal scaffold length and to identify the optimal proximal and distal landing zones. OCT after scaffold implantation can be invaluable to guide post-dilatation of the scaffold with properly sized non-compliant balloons to perfect strut apposition, taking into account the expansion limit of 0.5 mm for the Absorb BVS, especially in the initial experience of the operator.

Challenging lesions

Initial non-complex lesions studies had a very high procedural success rate. In a more real world setting lesion preparation, especially for more tortuous and calcified lesions, has proven to be necessary to obtain the same success rates. For truly calcified lesions, rotablation smoothens the atherosclerotic segments and is an invaluable technical aid for procedural success. For less calcified lesions, cutting balloons and the Scoreflex balloon have proven to be of value to appropriately prepare the lesion with full expansion of the pre-dilatation balloons and percentage diameter stenosis <40% before BVS implantation. In tortuous vessels the GuideLiner™ or Guidezilla™ guide extension catheters are valuable to increase back-up support and device deliverability. One should keep in mind that these 'aid-devices' have smaller inner lumens. The 5-in-6F guide extension catheter supports the Absorb BVS 2.5 mm and 3.0 mm only after preloading. For the Absorb BVS 3.5 mm a 6-in7F guide extension catheter is necessary.

Bifurcation lesions

Bifurcation lesions in appropriately selected patients are potentially good candidates for BVS treatment. In these, provisional stenting is the preferred strategy. If side branch treatment is necessary, the proximal optimization technique (POT) and side branch fenestration with a 2.0 or 2.5 mm balloon at low pressures (max. 8 atms) and final POT is advocated. If balloon fenestration of the side branch is insufficient, eventual bail-out post-dilatation with an undersized balloon and/or scaffolding of the side branch with

another BVS or DES and final POT could be needed. Fenestration of side branches with 2.0 mm and 2.5 mm non-compliant balloons has been tested *in vitro* without strut fractures and is considered safe by many operators. Just like metallic stents, scaffold deformation with local malapposition does happen for which post-dilatation is important. As overexpansion capabilities of the Absorb BVS are limited, classical, simultaneous kissing balloon post dilatation is not recommended. Final invasive imaging optimization is encouraged. Using BVS, we do not advocate techniques such as the culotte or crush techniques as these could result in ≥3 layers of stent struts (≥450 μ) with possible compromise of the lumen of the main branch and a high chance of delayed healing of intraluminal uncovered scaffold struts. At this moment the data on BVS bifurcation techniques are still limited compared to metal alloy stent bifurcation techniques.

Antiplatelet therapy post PCI

Current guidelines for antiplatelet therapy post PCI with DES advise Dual AntiPlatelet Therapy (DAPT) 6 to 12 months for stable angina. For ACS patients, based on the ESC non-STEMI and STEMI guidelines a minimum of 12 months DAPT is advised, preferably with prasugrel or ticagrelor [14-15]. Some new publications suggest that for second generation DES, DAPT duration might be shortened [16]. However, most of these studies are retrospective analyses and only a limited number of patients have been analyzed for shorter DAPT treatment. For the ABSORB BVS a minimum of 6 months DAPT was stated per protocol, and the majority of patients were on DAPT for 12 months. Based on the design where strut thickness of the ABSORB BVS is similar to first generation DES, and regarding initial reports on the occurrence of early as well as late stent thrombosis, the best advice for the moment is to prescribe DAPT for 12 months for all patients with ABSORB BVS and to avoid implantation of the ABSORB BVS in patients with a strict indication for oral anticoagulation as there is currently no data for shorter DAPT in patients on anticoagulants.

CONCLUSIONS

At the start of this new era in interventional cardiology, treating physicians should realize their responsibility for a careful introduction of the technology. This includes the preparation phase and a close follow-up phase for which both the NVVC and the Dutch Order of Medical Specialists have valuable guidelines.

Based on currently reported data and the experience of the authors with the Absorb BVS, some suggestions for the selection of patient and lesion characteristics for correct clinical indications as well as some useful implantation tips and tricks have been made.

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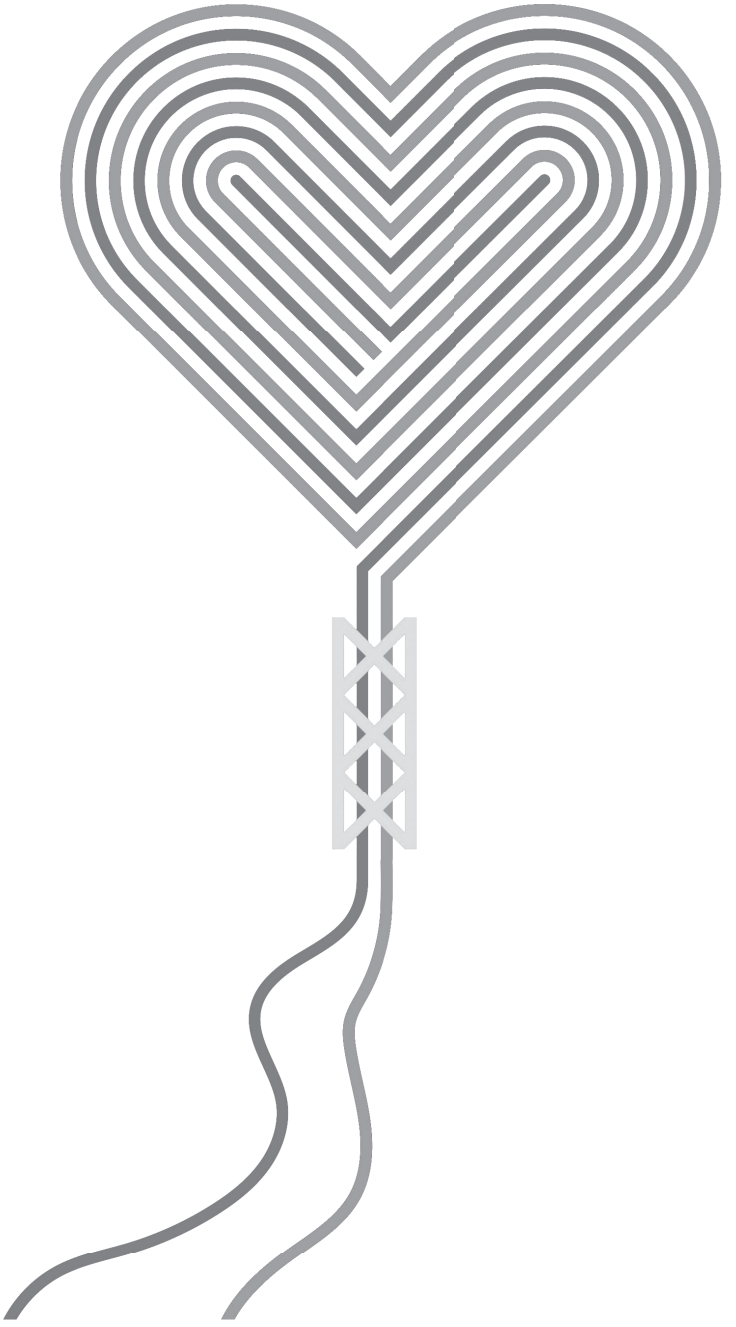

Part I

Early outcomes using different quantitative techniques in high risk lesions

Chapter 3

Expanded clinical use of everolimus eluting bioresorbable vascular scaffolds for treatment of coronary artery disease.

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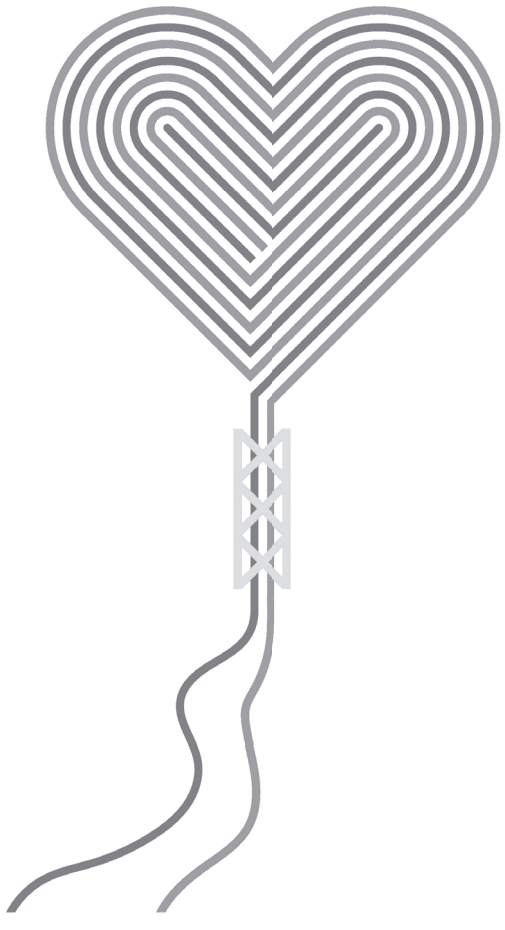

ABSTRACT

Background

Limited data are currently available on the performance of everolimus-eluting bioresorbable vascular scaffold (BVS) for treatment of complex coronary lesions representative of daily practice.

Methods

This is a prospective, mono-center, single-arm study, reporting data after BVS implantation in patients presenting with stable, unstable angina, or non-ST segment elevation myocardial infarction caused by de novo stenotic lesions in native coronary arteries. No restrictions were applied to lesion complexity. Procedural results and 12-month clinical outcomes were reported.

Results

A total of 180 patients have been evaluated in the present study, with 249 treated coronary lesions. Device Success per-lesion was 99.2%. A total of 119 calcified lesions were treated. Comparable results were observed among severe, moderate and non-calcified lesions in term of %diameter stenosis (%DS) (20.3±10.5%, 17.8±7.7%, 16.8±8.6%; p=0.112) and acute gain (1.36±0.41mm, 1.48±0.44mm, 1.56±0.54 mm; p=0.109). In bifurcations (54 lesions), side-branch ballooning after main vessel treatment was often performed (33.3%) with low rate of side-branch impairment (9.3%). A total of 29 cases with coronary total occlusions were treated. After BVS implantation %DS was not different from other lesion types (17.2±9.4%, vs 17.7±8.6%; p=0.780). At one year, all-cause mortality was reported in 3 cases. A total of 5 target lesion revascularizations and 4 non-target vessel revascularisations were reported. Four cases of definite scaffold thrombosis occurred.

Conclusions

The implantation of the everolimus-eluting bioresorbable vascular scaffold in an expanded range of coronary lesion types and clinical presentations was observed to be feasible with promising angiographic results and mid-term clinical outcomes.

INTRODUCTION

The everolimus-eluting bioresorbable vascular scaffolds (BVS) represent a novel approach for treatment of coronary artery disease. Similarly to conventional metal stents the absorb BVS provide acute lumen gain, vessel scaffolding and drug elution to the vessel wall immediately after implantation.[1] However, at variance with standard stents, the polymeric structure of this device allows a gradual bioresorption of the implant over time.[2] Complete scaffold bioresorption is hypothesized to offer several advantages over permanent metal devices comprising re-acquirement of physiological vasomotion, late lumen enlargement, non-invasive imaging and future treatment with bypass grafting.[3-5] In addition the absence of a foreign body could avoid phenomena such as permanent side-branch jailing, late acquired malapposition and the occurrence of late and very late stent thrombosis.[5]

The absorb BVS has been initially tested in humans in two cohort studies, both showing promising results in terms of surrogate and clinical endpoints.[6-9] However, being those studies an early evaluation of this technology, they were characterized by a patient population showing stable coronary artery disease and relatively simple lesions. The first randomized data in selected patients (Absorb II, Absorb Japan) supported the further development of this technique.

At the current state of the art, very limited data are available on BVS performance in real-world patients, including those presenting with acute coronary syndromes and complex lesions. A lack of information is especially evident when considering important lesion subsets such as calcified plaques, long lesions, bifurcations, and total occlusions.

Given this background, the present study aims to report angiographic and clinical data after an expanded clinical use of the second generation BVS, implanted in patients admitted with different clinical presentations including acute coronary syndromes and having a broad range of coronary lesion types.

METHODS

This is an investigator initiated, prospective, single-centre, single-arm post market study, aiming to evaluate the feasibility safety and performance of the absorb BVS for treatment of patients with coronary artery disease in routine clinical practice. Enrolled patients were subjects presenting with stable, unstable angina, or non-ST segment elevation myocardial infarction caused by de novo stenotic lesions in native coronary arteries. No restrictions were applied to lesion complexity. Due to the absorb BVS size availability, a Dmax (proximal and distal mean lumen diameter) within the upper limit of 3.8 mm and the lower limit of 2.0 mm by online QCA was required. Exclusion criteria

were minimal and comprised allergies or contraindications to antiplatelet medication, female patient with childbearing potential or currently breastfeeding, acute ST segment elevation myocardial infarction and post CABG patients. As per hospital policy patients with a previously implanted metal DES in the intended target vessel were also excluded. Also, although old age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age. A hybrid approach combining BVS with small DES or large DES where necessary was also not recommended.

All patients were treated with DAPT according to current guidelines. DAPT was prescribed for one year after PCI. Prasugrel was standard therapy for ACS presenting patients while clopidogrel was initiated for stable angina patients only.

To assess clinical outcomes, a questionnaire was sent to all living patients with specific queries on re-hospitalization and cardiovascular events. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary.

Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC, and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. The BVS received the CE mark for clinical use, indicated for improving coronary lumen diameter in patients with ischemic heart disease due to de novo native coronary artery lesions with no restriction in terms of clinical presentation. Therefore the BVS can be currently used routinely in Europe in different settings without a specific written informed consent in addition to the standard informed consent prior to the procedure. Therefore, a waiver from the hospital Ethical Committee was obtained for written informed consent, as according to Dutch law written consent is not required, if patients are not subject to acts other than as part of their regular treatment. Specific written informed consent post procedure was asked for a detailed follow-up program.

Study device

The device used in the present study is the second generation Absorb BVS (Abbott Vascular, Santa Clara, CA, USA); a balloon expandable scaffold with a polymer backbone of Poly-L lactide Acid (PLLA) coated with a thin layer of a 1:1 mixture of an amorphous matrix of Poly-D and L lactide acid (PDLLA) polymer, controlling the release of 100 micrograms/cm^2 of the anti-proliferative drug everolimus. Two platinum markers located at each Absorb BVS edge allowing for accurate visualization of the radiolucent Absorb BVS during angiography or other imaging modalities. Approximately 80% of the drug

is eluted within the first 30-days. Both PLLA and PDLLA are fully bioresorbable. The polymers are degraded mainly via hydrolysis resulting oligomers of lactate metabolized by Krebs cycle. Small particles, less than 2 μm in diameter, have also been shown to be phagocytised and degraded by macrophages.

Definitions

Device Success was defined as the attainment of <30% final in segment residual stenosis after absorb BVS implantation, by angiographic visual estimation. Procedure Success was defined as device success and no major peri-procedural complications (Emergent CABG, coronary perforation requiring pericardial drainage, residual dissection impairing vessel flow – TIMI-flow II or less -). Clinical success was defined as procedural success and no in-hospital major adverse cardiac events (MACE). All deaths were considered cardiac unless an undisputed non-cardiac cause was identified. Myocardial infarction (MI) and scaffold thrombosis were defined according to the Academic Research Consortium (ARC) definition. Any Target lesion revascularization (TLR) was defined as clinically driven if at repeat angiography a diameter stenosis >70% was observed, or if a diameter stenosis >50% was present in association with recurrent angina pectoris; objective signs of ischaemia (ECG changes) at rest or during exercise test, likely to be related to the target vessel; abnormal results of any invasive functional diagnostic test.

Target lesion failure was defined as the composite of cardiac death, target vessel myocardial infarction, or ischemia driven target lesion revascularization. Major adverse cardiac events (MACE), defined as the composite of cardiac death, any re-infarction (Q or Non Q-Wave), emergent bypass surgery (CABG), or clinically driven target lesion revascularization (TLR). Target vessel failure (TVF) was defined as cardiac death, target vessel myocardial infarction (MI), or clinically driven target vessel revascularization (TVR). Delivery failure was defined as opening of scaffold from its cover and insertion into the guiding-catheter without final implantation.

All potential events were adjudicated by a local independent Clinical Events Committee (CEC).

Quantitative coronary angiography

Quantitative coronary angiography (QCA) analyses were performed using the Coronary Angiography Analysis System (Pie Medical Imaging, Maastricht, Netherlands).

The QCA measurements we performed pre and post BVS implantation. The 37 μm platinum radio-markers located at each end of the Absorb BVS aided in the localisation of the non-radio-opaque scaffold for QCA. Analysed parameters included reference vessel diameter (RVD) - calculated with interpolate method - percentage diameter stenosis (%DS) and minimal lumen diameter (MLD). Acute gain was defined as post-procedural MLD minus pre-procedural MLD. The angiographic analysis were performed by three

investigators (YI, YO and RD) who were extensively trained in an experienced core-lab (Cardialysis BV, Rotterdam, The Netherlands)

A calcified coronary culprit lesion was defined as already reported[10] 'readily apparent densities noted within the apparent vascular wall at the site of the stenosis.' By qualitative assessment of the angiograms, target lesions were classified as severe ('radioopacities noted without cardiac motion prior to contrast injection generally involving both sides of the arterial wall'), moderate ('densities noted only during the cardiac cycle prior to contrast injection'), or none/mild (lesions other than severe and moderate calcified lesions). The Inter- and intra-observer variability in the qualitative analysis of coronary calcium on coronary angiograms have been already reported. [11]

To provide insights on the coronary bifurcation treatment with BVS we performed a full analysis of techniques and material used and we reported the occurrence of side-branch impairment, an end-point already reported in the literature as "side-branch trouble"[12] and defined as follow: at least 1 of the following procedural parameters: 1) Side-branch TIMI flow grade <3 after main vessel stenting; 2) need of guide-wire(s) different from the workhorse wire to rewire side-branch after main vessel scaffolding; 3) failure to rewire the side-branch after main vessel scaffolding; or 4) failure to dilate the side-branch after main vessel scaffolding and side-branch rewiring.

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation; p values were calculated with Fisher's Exact test for binary variables, Wilcoxon's Rank Sum test for continuous variables. Comparisons among multiple means were performed with analysis of variance (1-way ANOVA). A p value<0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 15.0 for windows (IL,US).

RESULTS

From September 2012 to July 2013 a total of 1529 percutaneous coronary interventions were performed in our center. A total of 180 patients have been enrolled in the present study, with 249 treated coronary lesions (Table 1). A total of 1157 patients were treated with standard second generation drug eluting stents. The remaining cases were treated with bare metal stents, dedicated bifurcation stents, balloon angioplasty only or thrombectomy only. Baseline clinical characteristics of the patients implanted with bioresorbable devices compared with those of the patients implanted with second generation drug eluting metal stents are reported in the supplement (Table 4). We observed that patients treated with bioresorbable devices were overall younger, more frequently

smokers, and had a lower rate of prior myocardial infarction, PCI and CABG. Therefore, this patient population is slightly different from the general population treated with percutaneous coronary intervention in everyday practice. However, the observed differences are in line with the predefined exclusion criteria.

Seventy-three patients (40.6%) showed multivessel disease. A total of 109 lesions (43.8%) were classified as type B2 or C, mean lesion length was 25.86 mm, bifurcation lesions with side-branch ≥ 2 mm were 54, a total of 119 lesions were defined with severe or moderate calcification and in 29 cases was present a total occlusion (Table 1).

Lesion preparation was performed in a large part of the cases mainly through balloon pre-dilatation (89.2%); rotational atherectomy was necessary in 4.8% of cases. Multiple scaffold implantations per lesion were allowed and often performed, (31.7%) up to the implantation of 5 scaffolds.

Table 1 Baseline clinical and lesion characteristics

Clinical characteristics	**N = 180**
Age	60.6 ± 10.6
Male n. (%)	134 (74.4%)
Hypertension n. (%)	94 (52.2%)
Hypercholesterolemia n. (%)	84 (46.7%)
Diabetes n. (%)	32 (17.8%)
Smoke n. (%)	99 (55.0%)
Peripheral vascular disease n. %	19 (10.6%)
CVA n. (%)	14 (7.8%)
Kidney disease n. (%)	11 (6.1%)
Prior MI n. (%)	30 (16.7%)
Prior PCI n. (%)	17 (9.4%)
Prior CABG n. (%)	0 (0.0%)
COPD n. (%)	11 (6.1%)
History of heart failure n. (%)	10 (5.6%)
Lesion characteristics	**L= 249**
One vessel disease	107 / 180 (59.4%)
Two vessel disease	61 / 180 (33.9%)
Three vessel disease	12 / 180 (6.7%)
Number of Treated Lesions per vessel (%)	
0 lesion	1/ 249 (0.4%)
1 lesion	189 / 249 (75.9%)
2 lesions	54 / 249 (21.7%)
3 lesions	4 / 249 (1.6%)
4 lesions	1 / 249 (0.4%)

Table 1 Baseline clinical and lesion characteristics (*continued*)

Lesion characteristics	L= 249
Lesion Location (%)	
LAD	120 / 249 (48.2%)
LCX	55 / 249 (22.1%)
RCA	66 / 249 (26.5%)
Diagonal	7 / 249 (2.8%)
LMCA	1 / 249 (0.4%)
AHA/ACC Lesion Classification (%)	
A	38 / 249 (15.3%)
B1	103 / 249 (41.4%)
B2	63 / 249 (25.3%)
C	46 / 249 (18.5%)
Lesion length (mm)	25.86 ± 13.64
Range min, max (mm)	5.32 - 80.01
Bifurcation lesion n. (%)	54 / 249 (21.7%)
Total occlusion (%)	29 / 249 (11.6%)
Calcification lesion (%)	119/ 249 (47.8%)

CVA= cerebrovascular accident; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease. Data are expressed as mean ± standard deviation or number and proportion

No scaffold dislodgment was reported. Bailout with drug eluting metal stents was performed in only 2 cases. Balloon post-dilatation was performed in a remarkable percentage of cases (45.0%) with often a balloon/scaffold ratio > 1.0 (41.8%). (Table 2) The overall device, procedure and clinical success rates per lesion, were respectively 99.2%, 98.8% and 98.8%

Table 2 Procedural data per-lesion analysis

Lesion characteristics	L= 249
Number of Scaffold or stent – per lesion (%)	
Average	1.41± 0.75
0 scaffold or stent	1 / 249 (0.4%)
1 scaffold or stent	169 / 249 (67.9%)
2 scaffolds or stents	61 / 249 (24.5%)
3 scaffolds or stents	10 / 249 (4.0%)
4 scaffolds or stents	7 / 249 (2.8%)
5 scaffolds or stents	1 / 249 (0.4%)
Overlapping	78
Overlapping BVS-BVS	76
Overlap scaffolds diameters 3.5mm-3.5mm,n (%)	20 (26.3%)
Overlap scaffolds diameters 3.5mm-3.0mm,n (%)	15 (19.7%)
Overlap scaffolds diameters 3.5mm-2.5mm,n (%)	3 (3.9%)

Table 2 Procedural data per-lesion analysis (*continued*)

Lesion characteristics	**L= 249**
Overlap scaffolds diameters 3.0mm-3.0mm,n (%)	15(19.7%)
Overlap scaffolds diameters 3.0mm-2.5mm,n (%)	15 (19.7%)
Overlap scaffolds diameters 2.5mm-2.5mm,n (%)	8 (10.5%)
Overlapping BVS-Metal	2 (2.6%)
Bailout scaffold/stent (%) – per lesion	
with BVS	8 / 249 (3.2%)
with Metallic stent	2 / 249 (0.8%)
Pre dilatation (%)	222 / 249 (89.2%)
Type of pre-dilatation balloon*	
Non-compliant	16 / 203 (7.9%)
Semi-compliant	187 / 203 (92.1%)
The usage of scoring (scoreflex or cutting)	9 / 219 (4.1%)
Average size of balloon	2.52 ± 0.36
Balloon / artery (pre-RVD) ratio < 1 (excluding total occlusion before procedure)	100 / 184 (54.3%)
Balloon / scaffold ratio ≤1	198 / 202 (98.0%)
Balloon 0.5mm smaller ≤ scaffold size	172/202 (85.1%)
Max pressure	13.95 ± 2.86
Use of other devices for lesion preparation	
Rotational atherectomy	12 / 249 (4.8%)
Manual thrombectomy	11 / 249 (4.4%)
Daughter catheter	5 / 249 (2.0%)
Buddy wire	18 / 249 (7.2%)
Post-dilatation (%)	112 / 249 (45.0%)
Type of post-dilatation balloon**	
Compliant	32 / 110 (29.1%)
Non-compliant	78 / 110 (70.9%)
Average size of balloon	3.27 ± 0.46 mm
Max pressure	15.58± 3.46
Balloon / Artery < 1	25 / 110 (22.7%)
Balloon > Scaffold size	46 / 110 (41.8%)
Balloon > Scaffold size+0.25mm	15 / 110 (13.6%)
Device success per lesion (%)	247 / 249 (99.2%)
Procedure success per lesion (%)	246 / 249 (98.8%)
Clinical success per lesion	246 / 249 (98.8%)
QCA pre-procedure	
RVD (mm)	2.63 ± 0.43
MLD (mm)	0.90 ± 0.35
% DS (%)	64.8 ± 14.5
Proximal Dmax (mm)	3.92 ± 8.28
Distal Dmax (mm)	2.89 ± 2.31

Table 2 Procedural data per-lesion analysis (*continued*)

Lesion characteristics	L= 249
QCA Post-procedure In-scaffold	
RVD (mm)	2.89 ± 0.42
DS (%)	17.6 ± 8.65
MLD (mm)	2.41 ± 0.41
Scaffold length	29.44± 15.71
Acute gain (mm)	1.51 ± 0.49
TIMI grade 2	2 / 249 (0.8%)
TIMI grade 3	247 / 249 (99.2%)

*Type of pre-dilatation balloon is reported in a subgroup of 203 patients. ** Type of post-dilatation balloon is reported in a subgroup of 110 patients. Data are expressed as mean ± standard deviation or number and proportion

QCA analysis

The mean pre-procedure reference vessel diameter (RVD) was 2.63 ± 0.43 mm, with a mean percentage diameter stenosis (%DS) of 64.8 ± 14.5% and a mean minimal lumen diameter (MLD) equal to 0.90 ± 0.35 mm. Post-procedure %DS was 17.60 ± 8.65 % with a mean MLD equal to 2.41 ± 0.41 mm reflecting a mean acute gain of 1.51 ± 0.49 mm. TIMI 3 flow was observed in 99.2% of the final angiograms. (Table 2, Figure 1)

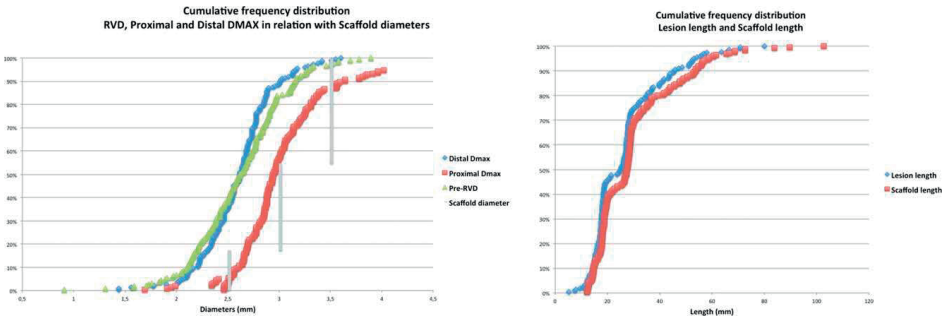

Figure 1 Vessel and scaffold diameters and lengths
Left panel, Cumulative frequency distribution of the reference vessel diameter the proximal end distal diameter in relation with the nominal size of the implanted scaffolds. Right panel, Cumulative frequency distribution of the lesion length in relation with the length of the implanted scaffolds

Bifurcation Lesions

A total of 54 lesions were located at the site of a bifurcation with a side-branch ≥ 2.0 mm. In 51 cases a provisional side branch technique was used, in addition 1 T-stenting, 1 culotte, 1 T-stenting with small protrusion (TAP) techniques were performed. In 18 cases side-branch wire protection was used, pre-dilatation and post-dilatation of the main vessel was often performed. Side-branch dilatation post MV stenting was necessary in

18 lesions. A final TIMI flow <3 in the main vessels (MV) was observed in only one case, in the side-branch this was reported in 3 lesions. Failure to re-wire the side-branch was never reported but in one case the operator was unable to re-cross the scaffold with a small balloon of 1.5 mm in diameter. (Table 5 Supplement) The overall rate of side-branch impairment was 9.3% (5/54)

Calcified lesions

A total of 119 calcified lesions were treated with BVS, 33 with severe calcification, 86 with moderate calcification, (Figure 2) and compared with non-calcified lesions. After treatment no differences were observed between calcified and non-calcified lesions in terms of MLD (Severe calcified 2.38 ± 0.38 mm, moderate calcified 2.41 ± 0.39 mm, non-calcified 2.42 ± 0.43 mm; p=0.889), %DS (Severe calcified 20.3 ± 10.5 %, moderate calcified 17.8 ± 7.7%, non-calcified 16.8 ± 8.6%; p=0.112) and acute gain (Severe calcified 1.36 ± 0.41mm, moderate calcified 1.48 ± 0.44 mm, non-calcified 1.56 ± 0.54 mm; p=0.109). These results were achieved with an overall higher use of buddy wires in calcified lesions (severe calcified 18.2%, moderate calcified 9.3%, non-calcified 3.0%; p=0.016)

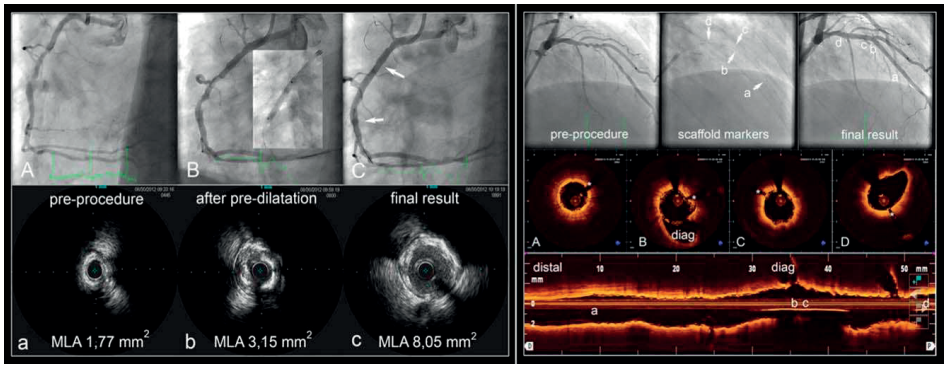

Figure 2 Calcified lesion and long lesions

Right panel. Calcified lesions. Angiogram showing a long lesion in the RCA (panel A). IVUS pre-procedure (Panel a) shows at the MLA more than 180 degrees superficial calcium (*). Panel B shows the angiogram after pre-dilatation (semi-compliant balloon 3.0 x 20mm). IVUS (panel b) shows clear "cracks" in the calcium (arrowheads), reducing the plaque resistance, thus sufficiently prepared for BVS implantation. Panels C and c show respectively the result on angiogram and on IVUS after implanting a BVS 3.5 x 28mm. Left panel. Long lesions. The angiogram top left shows the long lesion in the LAD. The mid-panel shows the markers of the two overlapping scaffolds (a & c distal BVS 3.0 x 28mm and b & d proximal BVS 3.5 x 18mm). The top right shows the final result with the OCT cross-section positions indicated by a to d). OCT (St.Jude Lightlab Dragonfly™) shows a well deployed scaffold. Panels B & C show the markers of respectively the proximal and distal scaffolds (*), indicating an overlap of approximately 1 mm.

Lesion preparation was more aggressive in calcified lesions with a higher use of rotational atherectomy (severe calcified 18.2%, moderate calcified 4.7%, non-calcified 1.5%; p<0.001) and scoring balloons (severe calcified 15 .2%, moderate calcified 3.5%, non-calcified 0.8%; p=0.001). Success rates were high in calcified vessels showing no significant differences when compare do non-calcified ones. Device success in severe calcified lesions was 97.0%, in moderate calcified 100% and in non-calcified 99.2%; p=0.251. (Table 3)

Total Occlusions

Vessels showing a total occlusion were 29. After vessel recanalization BVS implantation was performed achieving a final MLD and %DS not different from other lesion types (MLD: 2.51 ± 0.53 mm vs 2.40 ± 0.39; p=0.163; %DS: 17.2 ± 9.4% vs 17.7 ± 8.6%; p=0.780), with a high rate of final device success (96.6% vs 98.2%; p=0.465) and procedure success (96.6% vs 98.6%; p=0.393). To reach those results supportive wires were used much more frequently in occluded vessels (54.2% vs 2.1%; p<0.001). (Table 3, Figure 2)

Table 3 BVS implantation in calcified and total occluded lesions

Calcified lesions	**Severe calcification (L = 33)**	**Moderate calcification (L =86)**	**No calcification (L =130)**	**P value**
Lesion preparation				
Rotational atherectomy ,% (n)	18.2% (6/33)	4.7% (4/86)	1.5% (2/130)	<0.001
Scoring balloon ,% (n)	15.2% (5/33)	3.5% (3/86)	0.8% (1/130)	0.001
Daughter catheter ,% (n)	3.0% (1/33)	2.3% (2/86)	1.5% (2/130)	0.886
Buddy wire,% (n)	18.2% (6/33)	9.3% (8/86)	3.0% (4/130)	0.016
Average size of balloon	2.48 ± 0.38	2.55 ± 0.35	2.52 ± 0.36	0.702
Non-compliant balloon ,% (n)	13.3% (4/30)	9.5% (7/74)	5.1% (5/99)	0.276
QCA pre-procedure				
RVD (mm)	2.51 ± 0.35	2.66 ± 0.43	2.64 ± 0.46	0.256
MLD (mm)	0.97 ± 0.40	0.92 ± 0.36	0.87 ± 0.34	0.358
% DS (%)	62.3 ± 13.5	65.0 ± 12.6	65.3 ± 15.7	0.592
Lesion length	36.11 ± 2.34	27.99 ± 1.54	22.11 ± 1.16	<0.001
QCA post-procedure				
RVD (mm)	2.97 ± 0.38	2.93 ± 0.39	2.85 ± 0.46	0.244
MLD (mm)	2.38 ± 0.38	2.41 ± 0.39	2.42 ± 0.43	0.889
% DS	20.3 ± 10.5	17.8 ± 7.7	16.8 ± 8.6	0.112
Acute gain (mm)	1.36 ± 0.41	1.48 ± 0.44	1.56 ± 0.54	0.109
Device success per lesion, % (n)	97.0% (32/33)	100% (86/86)	99.2% (129/130)	0.251
Procedure success per lesion, % (n)	97.0% (32/33)	98.8% (85/86)	99.2% (129/130)	0.571
Clinical success (per lesion), % (n)	97.0% (32/33)	98.8% (85/86)	99.2% (129/130)	0.571

Table 3 BVS implantation in calcified and total occluded lesions *(continued)*

Occluded vs non-occluded	Occluded (L =29)	Non-occluded (L = 220)	P value
QCA post-procedure			
RVD (mm)	3.01 ± 0.47	2.88 ± 0.41	0.103
MLD (mm)	2.51 ± 0.53	2.40 ± 0.39	0.163
% DS (%)	17.2 ± 9.4	17.7 ± 8.6	0.780
Acute gain (mm)	-	1.51 ± 0.49	-
Procedural characteristics			
Daughter catheter, % (n)	3.4% (1/29)	1.8% (4/220)	0.465
Buddy wire, % (n)	10.3% (3/29)	6.8% (15/220)	0.449
Type of first wire (after recanalization)			
Supportive	54.2% (13/ 24)	2.1% (4/195)	<0.001
Non-supportive	45.8% (11/24)	97.9% (191/195)	<0.001
Device success after recanalization, % (n)	100% (29/29)	99.1% (218/220)	1.0
Procedure success after recanalization, % (n)	100% (29/29)	98.6% (217/220)	1.0
Clinical success after recanalization, % (n)	100% (29/29)	98.6% (217/220)	1.0

Data are expressed as mean ± standard deviation or number and proportion

Long Lesions

In a total of 79 lesions (31.7%) more than one device was implanted (Figure 1, Figure 3). The mean lesion length treated with BVS was 25.86 ± 13.64 mm. The maximum lesion length covered by BVS was 80.01 mm. Overlapping of BVS with BVS was often performed with a total of 76 overlapping scaffolds. The great majority (96%, 73/76) were performed using scaffold of the same diameter or with a maximum of 0.5 mm difference in nominal diameter. In 3 cases a 3.5 mm scaffold was placed in overlap with a 2.5 mm device.

Clinical outcomes

Survival data at 12 months after the procedure were available for 99.4 % of patients. At 12-month follow-up all cause-death was reported in 3 cases. A total of 5 target lesion revascularizations and 4 non-target vessel revascularisations were reported. Four definite, scaffold thrombosis (ST) occurred within one year after index procedure; none of them was acute or sub-acute. Of note, one of those cases was meeting the ARC criteria for ST but no clear thrombus was observed by optical coherence tomography (OCT). In the remaining 3 cases, severe calcification, bifurcation lesion and long overlap were observed but BVS underexpansion was the factor that was present in all of them.

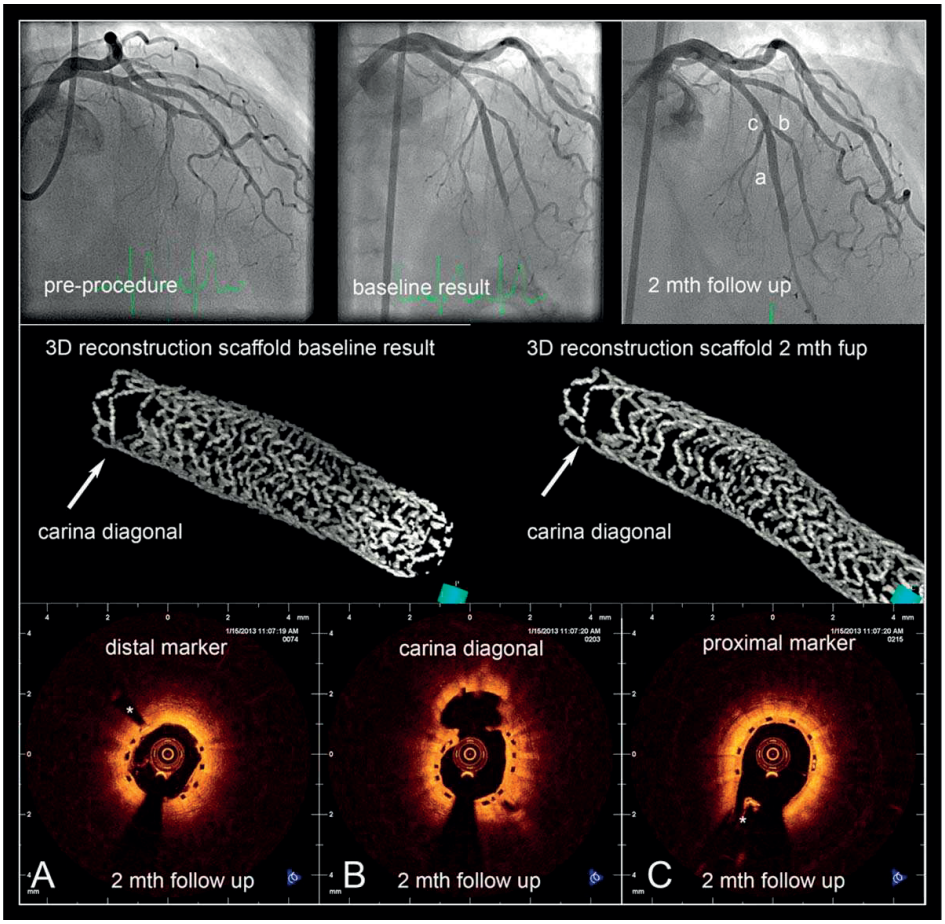

Figure 3 Chronic total occlusion and bifurcation

Top panels show from left to right the angiograms pre-procedure, after recanalization and scaffold implantation (BVS 3.0 x 28mm with the sequential post dilatation of the diagonal and the scaffold in the main branch) and 2-month follow-up with partial distal vessel positive remodelling. Characters a-c indicate the positions of the OCT cross-sections. OCT (St.Jude Lightlab Dragonfly™) post procedure show distal a well deployed scaffold (Panel A), a well opened carina with the diagonal branch (Panel B *) and the overlap of the proximal marker with the septal branch (Panel C *). The 3D reconstruction (Intage realia™, Cybersystems, Tokyo, Japan) shows the opening of the struts at the carina with the diagonal branch. (Arrowhead bottom panel).

DISCUSSION

The present investigation represents an evaluation of the feasibility of BVS implantation in everyday clinical practice reflected by in a wide range of coronary lesions subsets including bifurcations, calcified vessels, chronic total occlusions and long lesion in patients with stable coronary artery disease and acute coronary syndromes. At variance of

previous reports we also aimed to provide a detailed description of procedural data and techniques that were used to allow the use of this novel device in challenging subsets.

Bifurcation lesions

A common concern regarding this technology is the fact that implantation of the BVS in bifurcation lesions might result in side-branch compromise due to the thick strut nature of this device. In keeping with this concept, a recent study performed by our group showed that BVS deployment could be associated with an increased small (≤0.5 mm) side-branch occlusion and a consequent increase of enzymes release after procedure.[13]

However, in the present report the effect of BVS implantation in what is commonly considered a bifurcation lesion (with a side branch ≥ 2 mm) was specifically investigated.

Rewiring of the side-branch in those cases and consequent ballooning (mainly with small balloon 1.5-2 mm in diameter) of the SB ostium is feasible as we already reported[13] and safe also in terms of scaffold geometry and fracture.[14, 15] In the present study side-branch ballooning was performed in one third of the patients (33%, 18/54) with promising results. In majority of the cases this was done with sequential ballooning and proximal optimization technique (POT), kissing balloon only in 3 cases.

Taking into consideration the rates of TIMI flow < 3 in the main vessel or in the side-branch, the rate of failure to rewire the side-branch and failure to dilate the side-branch, the BVS performed at least as good as metallic if considering historical data. [12]

In addition the rate of the composite endpoint side-branch impairment (9.3%) was observed to be encouraging especially when compared with data recently reported by Burzotta et al. with rates of side-branch impairment in sirolimus- and everolimus-eluting stents respectively 16% and 11%. [12] These data are supportive of the concept that BVS could be used safely in bifurcation lesions with side-branch ≥ 2.0 mm with a single scaffold approach and could provide results similar to metallic stents.

Calcified lesions

A total of 119 calcified lesions with a considerable percentage of heavily calcified plaques, were treated with BVS. A large number of those lesions were located in diffusely diseased vessels with an overall mean treated lesion length of more than 36 mm (severe calcified group). QCA analysis showed a final MLD, %DS, acute gain and device, procedural and clinical success not different from non-calcified lesions. These results were obtained at the cost of a more aggressive lesion preparation with a considerable use of rotational atherectomy and scoring balloons.

Such approach is needed to facilitate the delivery of the scaffold given its slightly higher profile compared with second generation DES. In addition appropriate lesion preparation could avoid scaffold under-expansion or need for aggressive post-dilatation. This strategy could be relevant also when using metallic stents. [16] Our data might

suggest feasibility of BVS implantation in calcified vessels with optimal results given an adequate lesion preparation.

Although, many of the advantages proposed for BVS, namely the restoration of the vasomotion and vessel physiology could be minimized in calcified artery, patients with diffused calcified vessels have often also a multivessel disease;[17] in such scenario a temporary implant would allow future surgical treatments.

Total occlusions

Successful re-canalization of total occlusions has been previously associated with a significant improvement in angina symptoms [18, 19] and complete coronary revascularization was demonstrated to have an important impact on long-term clinical outcomes.[20]

Vessels with total occlusions have peculiar characteristics in terms of vascular remodelling; this is a dynamic process involving regulation of vascular cell migration and mitosis and apoptosis rates in response to several factors comprising blood flow and pressure, shear stress, circumferential stretch and wall tension.[21] Reduction or even more absence of blood flow in totally occluded vessels might promote negative remodelling and plaque growth; on the other hand restoration of flow could have an opposite effect.

Recently, Park J.J. and colleagues reported, at 6-month follow-up after successful total occlusion revascularization, a flow-dependent vascular remodelling process in human coronary arteries, associated with increases in lumen diameter, lumen area and external elastic membrane area.[22] This process was observed in a large part of treated vessels (69%) with a mean lumen diameter increase of 0.40 ± 0.34 mm. IVUS analysis of those vessels revealed that the amount of incomplete stent apposition increased significantly during 6 months in patients with positive remodelling and lumen area increase but not in those without lumen area increase.

In this scenario choosing a metal stent based on the vessel diameter at the index procedure might lead to stent under-sizing.

Given this background a theoretical advantage of BVS implantation in patients with total occlusion is the fact that it might allow at mid-term follow-up, after the loss of scaffold mechanical integrity, late lumen enlargement without late acquired malapposition, as at that time the remnants of the bioresorbable implant can follow the vessel remodelling.

Long lesions and overlap

In the present series several lesions were treated with more than one scaffold up to a maximum of 5 scaffolds for a maximum lesion length of 80 mm. Operators were advised to minimize the extension of overlapping segment using a marker-to-marker technique.

In the metal stent era, long segments treatment has been associated to an increased risk of stent thrombosis [23-25] and could results in prevention of future surgical revascularisations.

Both these issues could be overcome with the use of bioresorbable technologies and the introduction in the near future of bioresorbable scaffold with thinner struts could mitigate the effect of overlap on delayed vascular healing.

Clinical outcomes

The mid-term clinical outcomes of this study revealed a relatively reassuring safety profile of the BVS when used in a large range of lesion type and in patients with either stable symptoms or acute coronary syndromes. The event rate in this study is only minimally higher compared to the results in non-complex patients reported in the randomized Absorb II and Absorb Japan studies [26, 27]. In other European registries like GHOST-EU and AMC registries [28, 29] reporting early experience with BVS, the event rate was in slightly higher compared with more recent registries like the Milan registry [30] and ASSURE BVS [31] where more BVS specific implantation protocols where applied. Such observations suggest the relevance of a BVS dedicated implantation technique ensuring good lesion preparation and optimal scaffold deployment often facilitated by high pressure post-dilatation.

Regarding the occurrence of scaffold thrombosis (ST), at variance with previous reports no acute or sub-acute STs were observed in the present investigation. These findings could be related to procedural characteristics including a meticulous lesion preparation pre-BVS implantation and a reasonably high rate of post-dilatation.

The review of the cases with ST revealed that several factors might be associated with such events comprising severe lesion calcification, the presence of bifurcations, long overlap and antiplatelet therapy discontinuation. However, the factor that was particularly consistent was scaffold under-expansion. Previous investigations described stent underexpansion as an important predictor of ST with both bare metal stents and DES,[32-36] with an impact on the occurrence of ST that was hypostasized to be superior to stent malapposition.[37] The mechanisms behind these findings could be the fact that stent underexpansion translates into an abnormal shear stress. In particular increased radial transport of blood components and low wall shear stress, were described to promote platelet-dependent thrombosis.[38] In addition the impact of underexpansion on shear stress could be potentiated by the presence of the BVS thick struts.[39]

Although, given the small number of patients and events reported in the present study it is not possible to reach firm conclusions, our findings suggest that optimal BVS expansion, with lesion preparation and appropriate scaffold post-dilatation, should be pursued given the possible relevant clinical implications.

LIMITATIONS

The present report is an investigator initiated, single center, single arm study. The choice for BVS implantation was left to operator discretion; this could be source of selection bias. The absence of a comparator arm is limiting the interpretation of our data. The limited number of patients does not allow reaching firm conclusions on clinical outcomes. The mid-term follow-up is preventing the availability of information on long-term safety and efficacy.

CONCLUSION

The implantation of the everolimus-eluting bioresorbable vascular scaffold in an expanded range of coronary lesion types and clinical presentations was observed to be viable with promising angiographic results and mid-term clinical outcomes. Larger studies with longer follow-up and a direct comparison with currently available metallic drug eluting stents are needed to fully evaluate the possible additional value of the bioresorbable technologies an all comers setting.

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SUPPLEMENTAL MATERIAL

Description of the Scaffold thrombosis cases

Case 1: A 59-year old male patient, smoker, with history of cerebrovascular accident and stable angina pectoris, was treated after pre-dilatation of a long lesion involving the ostial left anterior descending (LAD) and the bifurcation with the first diagonal (D1), using a BVS 3.5 x 28mm. Despite a post-dilatation was performed with a 3.5 non-complaint (NC) balloon at high pressure, the BVS remained under-expanded with an impaired flow in the first diagonal. At day 111 post PCI the patient was re-admitted with NSTEMI, while being on DAPT, and angiographically was observed a total re-occlusion of the LAD beginning from the ostium. After pre-dilatation a DES 3.5 x32mm was implanted. Of note, at day 81 after the second PCI the patients was again re-admitted for instable angina pectoris caused by a re-occlusion also of the metal stent in the proximal LAD. The patient was treated with CABG.

Lesion key characteristics: Ostial lesion, long lesion, bifurcation, impaired side-branch TIMI flow and BVS underexpansion

Case 2: A 69-year old male with history of dyslipidaemia and hypertension was admitted with NSTEMI. Angiographically was observed a long, severely calcified, chronic total occlusion (CTO) of the proximal and mid LAD with severe calcification and involvement of D1. After Pre-dilatation, 2x 3.5 x 18mm BVS were implanted. The procedure was complicated by pinching of D1 and thrombus formation. Additional ballooning of the ostium of the side-branch was performed, but at the end of the procedure remained BVS underexpansion and haziness in the mid LAD. Despite continued DAPT usage the patient developed on day 47 a non-Q wave MI due to definite scaffold thrombosis in the proximal LAD, which was treated with thrombectomy and DES implantation.

Lesion key characteristics: CTO, long lesion, bifurcation, severe calcification, thrombus formation and BVS underexpansion

Case 3: A 65-year old male patient, smoker, with history of hypertension was admitted with NSTEMI, due to a sub-occlusive lesion in the LAD located at the site of a tortuous trifurcation with the first and second diagonal. The initial TIMI flow was 1. After pre-dilatation, a 3.0 x 18mm BVS was implanted and after post-dilatation a TIMI III flow was achieved. At day 142 on DAPT the patient was re-admitted with NSTEMI. Angiographically a proximal BVS edge sub-total restenosis was observed with a distal TIMI flow 1. A DES stent 3.5 x38mm was deployed covering the BVS and a large proximal segment. Of note, this case was meeting the ARC criteria for stent thrombosis and was adjudicated as such by the CEC, but should be mentioned that an OCT performed before pre-dilatation did not showed any clear intraluminal thrombus.

Lesion key characteristics: tortuous trifurcation (no thrombus by OCT)

Case 4: A 70-year old male, with severe peripheral vascular disease, diabetes mellitus, dyslipidaemia, hypertension, and reduced left ventricular function was admitted with stable angina pectoris. Angiography revealed, a long and severely calcified lesion mid LAD involving two bifurcations (D1 and D2). Aggressive preparation was performed with rotational atherectomy and high-pressure dilatations with NC and cutting balloons. Two overlapping BVS were placed with a quite long segment of overlap (5 mm). Despite extensive post-dilatation under-expansion remained at the end of the procedure. Five months after index PCI, the patient underwent non-cardiac surgery. The antiplatelet therapy was interrupted (both aspirin and clopidogrel) and the patient developed a NSTEMI due to a scaffold thrombosis that was treated with balloon dilatation and eptifibatide. Unfortunately, the patient died few days later because of heart failure.

Lesion key characteristics: Severe calcification, bifurcation, long overlap, no antiplatelet therapy and BVS underexpansion

Table 4 Baseline clinical characteristics

Clinical characteristics	N = 180	N=1157	
Age	60.6 ± 10.6	66.1 ± 11.7	<0.001
Male n. (%)	134 (74.4%)	850 (73.5%)	0.69
Hypertension n. (%)	94 (52.2%)	661 (57.1%)	0.54
Hypercholesterolemia n. (%)	84 (46.7%)	504 (43.6%)	0.18
Diabetes n. (%)	32 (17.8%)	231 (19.9%)	0.80
Smoke n. (%)	99 (55.0%)	481 (41.6%)	< 0.001
Peripheral vascular disease n. %	19 (10.6%)	101 (8.7%)	0.32
CVA n. (%)	14 (7.8%)	87 (7.5%)	0.73
Kidney disease n. (%)	11 (6.1%)	122 (10.5%)	0.06
Prior MI n. (%)	30 (16.7%)	305 (26.3%)	0.01
Prior PCI n. (%)	17 (9.4%)	358 (30.9%)	< 0.001
Prior CABG n. (%)	0 (0.0%)	118 (10.2%)	< 0.001
COPD n. (%)	11 (6.1%)	71 (6.1%)	0.81
History of heart failure n. (%)	10 (5.6%)	70 (6.0%)	0.74

CVA= cerebrovascular accident; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease. Data are expressed as mean ± standard deviation or number and proportion

Table 5 BVS implantation in Bifurcation lesions

Procedural characteristics	L=54
LAD	38
CX	12
RCA	4
Involvement of both SB and MV (Medina 111, 101, 011)	15 (27.8%)
1 Scaffold technique	51 (94.4%)
Provisional T	51 (94.4%)
T-stenting	1 (1.8%)
Culotte	1 (1.8%)
TAP	1 (1.8%)
MV pre-dilatation	44 (81.4%)
MV post-dilatation	26 (44.4%)
SB pre-dilatation	6 (11.1%)
SB dilatation post MV Scaffolding	18 (33.3%)
Kissing balloon	3 (5.6%)
Proximal optimization technique	26 (44.4%)
Final MV TIMI flow <3	1 (1.8%)
Side-branch TIMI flow <3	3 (5.6%)
Failure to rewire the SB	0 (0%)
Different wire from the workhorse to rewire SB after MV scaffolding	2 (3.7%)
Failure to dilate SB	1 (1.8%)
Composite of side-branch impairment	5 (9.3%)

Data are expressed as mean ± standard deviation or number and proportion

Chapter 4

Conformability in everolimus-eluting bioresorbable scaffolds compared with metal platform coronary stents in long lesions

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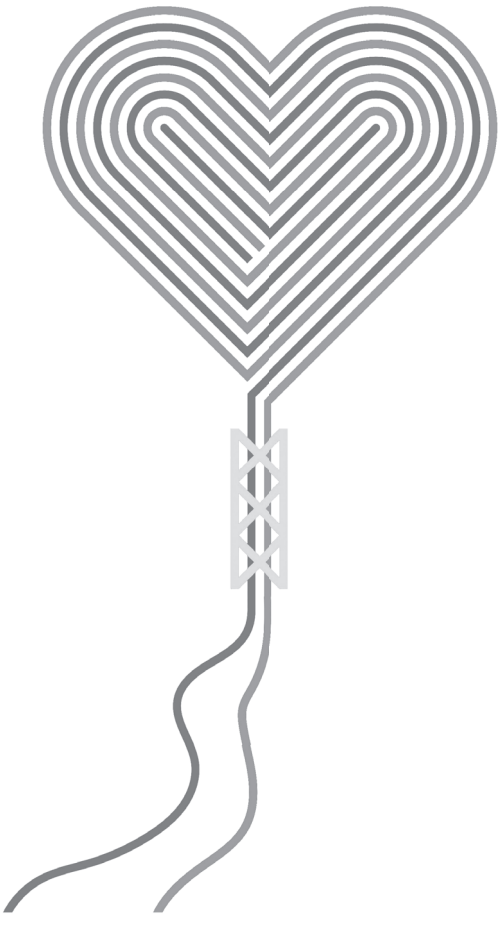

STRUCTURED ABSTRACT

Objectives

The aim of this study was to determine if there are significant differences in curvature of the treated vessel after the deployment of a polymeric BRS or MPS in long lesions.

Background

The impact of long polymeric Bioresorbable Absorb scaffolds (BRS) compared with metallic platform stents (MPS) on vessel curvature is unknown.

Methods

This retrospective study compares 32 patients who received a single everolimus-eluting BRS with 32 patients treated with a single MPS of 28mm. Quantitative coronary angiography (QCA) was used to evaluate curvature of the treatment and peri-treatment region before and after percutaneous coronary intervention (PCI).

Results

Baseline demographic and angiographic characteristics were similar between the BRS and MPS groups. Pre-treatment lesion length was 22.19 mm vs 20.38 mm in the BRS and MPS groups respectively (p=0.803). After treatment, there was a decrease in median diastolic curvature in the MPS group (from 0.257cm^{-1} to 0.199cm^{-1}, p= 0.001). A similar trend was observed in the BRS group but did not reach statistical significance (median diastolic curvature from 0.305cm^{-1} to 0.283cm^{-1}, p= 0.056). Median Percentage relative change in diastolic curvature was lower in the BRS group compared with the MPS group (BRS vs MPS: 7.48% vs 29.4%, p= 0.013). By univariate analysis, use of MPS was an independent predictor of change in diastolic curvature (p = 0.022).

Conclusions

In the deployment of long coronary scaffolds/ stents (28mm in length), BRS provides better conformability compared with MPS.

INTRODUCTION

The everolimus-eluting Bioresorbable Absorb scaffold (BRS) (Abbott Vascular, Santa Clara, California) represented a novel change in the treatment of coronary artery lesions. The BRS is composed of a poly-L-lactic acid (PLLA) - based platform which had been shown to provide similar outcomes to best-in-class metallic drug eluting stents (DES) [1]. Besides the ability to have complete strut resorption at 36 months, there are several potential benefits of BRS including no trigger for thrombosis after resorption and restoration of vasoreactivity [2]. Typically, implantation of hard metallic implants straightens the coronary artery and thus modifies its curvature. A previous computational study demonstrated that after implantation of a metallic implant in a coronary artery, the curvature of the stent edges alters significantly which correlate to the changes in shear stress distribution and potentially with the neointimal proliferation pattern [3]. As implantation of coronary stents/ scaffolds can alter blood rheology especially at the inflow and outflow edge of the stents, the vessel distortion post device implantation may contribute to early and late stent failure such as pertaining to stent fracture. Geometric changes in the arteries post implantation are largely determined by the conformability of the stent [4]. The conformability of the stent has been described as the flexibility of a stent in its expanded state with adaptation to the natural shape of the vessel. A higher conformability of the stent is associated with less potential for vessel distortion and trauma [5].

Previous studies using BRS in short lesions demonstrate better conformability and favorable clinical outcomes compared to MPS in the acute setting [6, 7]. In the study by Gomez Lara et al, the acute change in curvature and angulation as quantified by quantitative coronary angiographic analysis was decreased in BRS compared to MPS [change in region curvature- MPS vs BRS: 0.085 cm-1 vs 0.056 cm-1, p=0.06, angulation MPS vs BRS 6.4° vs 4.3°, p=0.03] [7] and was shown to recover on follow up [8]. This effect may be more pronounced and more relevant in a long lesion in either the coronary or peripheral arterial system. However, the acute effects of its implantation on vessel geometry in long coronary lesions are yet to be investigated. The aim of this study was to determine if there are any significant differences in terms of curvature of the treated vessel after the deployment of a polymeric scaffold device in long lesions and compare this to a MPS.

METHODS

Study design, population, and treatment device

This is a non-randomized, 2-arm, retrospective study performed with patients from the onging BVS Expand and BVS STEMI First registries that received a Everolimus Eluting BRS (BRS- Absorb; Abbott Vascular, Santa Clara, CA, US) compared with a subset of historical controls from the same institutional registries (X-SEARCH) who received a Cobalt Chromium- Everolimus Eluting Stent (CoCr-EES; XIENCE^{R} stent, Abbott Vascular, Santa Clara, CA, US).

In brief, the common inclusion criteria for this study are patients who had received a single BRS or CoCr EES that are 28mm in length in long coronary lesions. The patients in the BRS group are selected from the BVS Expand and BVS STEMI registries which are single centre prospective observational registries conducted at Thorax Centre, Erasmus Medical Centre that evaluates the long term safety and performance of the BRS-Absorb coronary stent in routine clinical practice post market registration. Informed, written consent was obtained from the patients before they undergo any procedure. The lesions are also more complex with more bifurcations and calcified lesions. From the X-SEARCH registry, patients with similar angiographic characteristics were selected for this study [9].

The BRS-Absorb vascular scaffold is a balloon-expandable device, consisting of a polymer backbone of PLLA coated with a thin layer of a 1:1 mixture of an amorphous matrix of PLLA polymer containing 100ug/cm2 of the antiproliferative drug everolimus. The implant is radiolucent but has 2 platinum markers at each edge that allow visualization on angiography and other imaging modalities. Physically the scaffold has struts with an approximate thickness of 150 um, which are arranged as in-phase zigzag hoops linked together by 3 longitudinal links (Figure 1A).

The metallic platform of the everolimus-eluting XIENCE^{R} family stent (EES) is composed of a cobalt chromium (CoCr) alloy. The platform has a design similar to the Absorb platform and consists of serpentine rings connected by links fabricated from a single piece (Figure 1B). The strut width of the CoCr-EES is 91um. The polymer and drug coating add a combined thickness of 7 um. The metallic platforms of the CoCr EES are constructed by a strut thickness of 81 um each [10].

Treatment procedure

Lesions treated with the BRS were implanted according to the procedural steps in line with the accepted recommendations at the time of the study. Predilation with either a semi-compliant or non-compliant balloon was highly encouraged. The BRS was implanted at a pressure not exceeding the rated burst pressure (16 atm). Post-dilation with either a semi-compliant or non-compliant balloon was performed at the discretion of

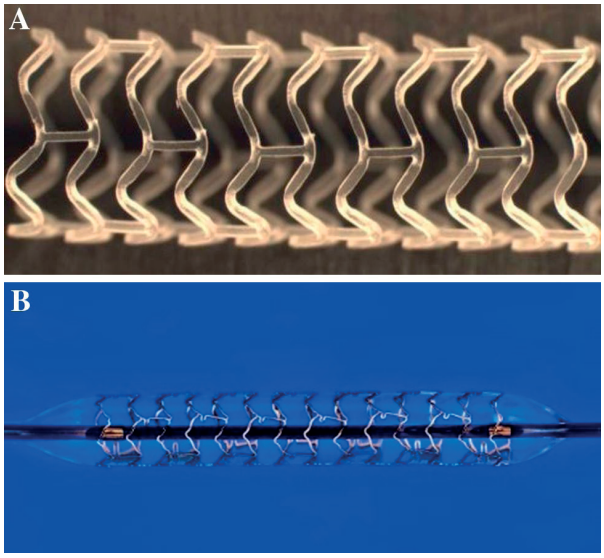

Figure 1A
a Bioresorbable scaffold: The second generation ABSORB-BVS (Abbott Vascular, Santa Clara, CA, USA) has a strut thickness of 150 µm, consisting of in-phase zigzag hoops linked by bridges. The device is radiolucent but has two radiopaque platinum markers at each proximal and distal edge that facilitate ease of visualization on angiography. b Cobalt chromium everolimus- eluting stent (CoCr EES- XIENCE^{R}, Abbott Vascular, Santa Clara, CA, US): The XIENCE^{R} are the metal platform stents and consist of a metallic platform made of cobalt chromium alloy. The struts are serpentine rings connected by links fabricated from a single piece. The XIENCE^{R} is covered by an everolimus coating

the operator. Patients were prescribed with standard guideline recommended medical therapy including at least 12 months' duration of dual antiplatelet therapy and antianginal therapy when appropriate.

Quantitative coronary angiography (QCA) evaluation

Angiographic views with minimal foreshortening of the lesion and limited overlap with other vessels were used whenever possible for all phases of the treatment: pre-procedural angiography, and after obtaining final result [11]. Comparison between pre and post treatment, were performed in matched angiographic views of 10 degrees or less. The 2-dimensional (2D) angiograms were analyzed with the CASS 5.10 analysis system (Pie Medical BV, Maastricht, the Netherlands). In each patient, the treated region and the peri-treated regions (defined by 5 mm proximal and distal to the device edge) were analyzed. The computer defined minimal luminal diameter, reference diameter obtained by an interpolated method, and percentage diameter stenosis in the post procedure angiogram.

The definition of "Curvature" is the infinitesimal rate of change in the tangent vector at each point of the centerline. This measurement has a reciprocal relationship to the radius of the perfect circle defined by the curve at each point. The curvature of the vessel is calculated as 1/radius of the circle in cm^{-1}, with a research program installed in the QCA Analysis software (CASS 5.10, Pie Medical Imaging) [12]. The segment of interest was defined as the stented/ scaffolded length. To enable analysis of curvature in the

same anatomical region, the scaffold position was superimposed on the pre-procedural angiogram (Figure 2). The software automatically detects the lumen contours of the selected segment and configures the centerline. Three points are then defined according to the centerline: 1 at the proximal, 1 at the distal, and 1 at the center of the defined segment. Next, a perfect circle is drawn through these points, calculating the radius of the circle and the curvature value. Prior to and after the procedure, the curvature of the segment of interest was repeatedly measured both during systole and diastole. Percentage relative change in curvature (Cv) was calculated as % (postCv- preCv)/preCv in the respective cardiac phases. Cyclic changes in vessel curvature were estimated as differences between systole and diastole at both pre-treatment and post-treatment.

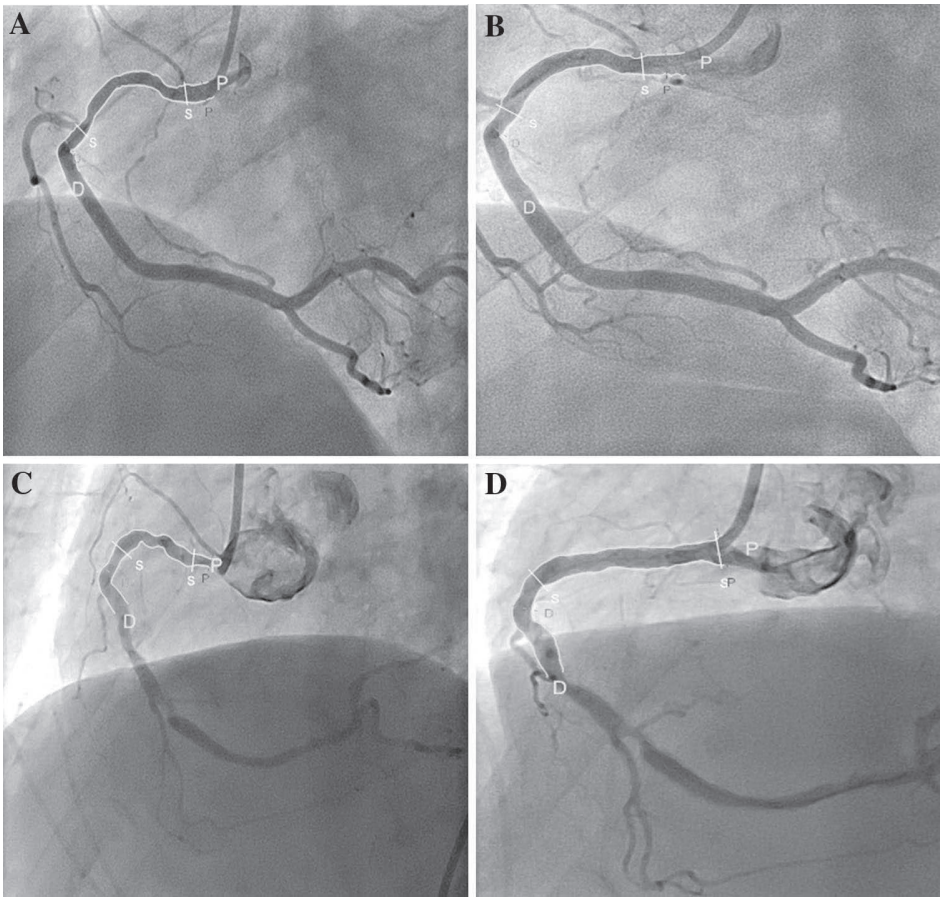

Figure 2 Curvature Analysis of the BRS and MPS
curvature analysis before and after deployment of a BRS (Fig. 2a, b) and a MPS (Fig. 2c, d). After implantation of a BRS, the curvature changed from 0.58 to 0.49 cm^{-1} whereas after the MPS was implanted, the curvature changed from 0.85 to 0.23 cm^{-1}. BRS bioresorbable scaffold, MPS metallic platform stent

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality assumptions of all continuous variables. Descriptive statistical analysis was performed with continuous variables expressed as median (interquartile range) and with categorical variables presented as counts (percentage). For comparison between groups, Mann-Whitney *U* test were used for the continuous variables. The chi-square test has been used to assess differences in categorical variables. Pre and post treatment comparisons within groups were assessed with Wilcoxon signed rank tests. Because the curvature, cyclic changes of curvature, and difference of curvature between pre- and post-treatment did not have a normal distribution, a log transformation was performed to achieve a normal distribution. A univariate analysis was performed between curvature and angulation changes with baseline demographic and angiographic variables. Variables that were found to be significant at the univariate level were tested with a multivariate linear regression model. (The thresholds for entry into and removal from the model were 0.1.) All statistical tests were carried out at the 5% level of significance. All analysis was performed by SPSS version 21 (SPSS, Inc., Chicago Illinois).

RESULTS

The baseline clinical and angiographic characteristics are shown in Table 1. A total of 64 patients were involved in this study of which 32 were treated with the BRS and 32 with the MPS. A flow chart summarizing patient selection is shown in Figure 3. There was no difference in median age [BRS vs MPS: 59.6 years vs 64.9 years, p=0.453)], gender or clinical presentation between the 2 device groups. There were no significant differences in the cardiovascular risk factors.

Table 1 Baseline clinical and angiographic characteristics

	BRS (N=32)	MPS (N=32)	p value
Age (years)	59.6 (52.5, 67.8)	64.9 (57.7, 70.7)	0.453
Men	22 (68.8)	22 (68.8)	1.000
Hypertension	18 (56.2)	20 (62.5)	0.611
Hypercholesterolemia	15 (46.9)	17 (53.1)	0.617
Diabetes mellitus	5 (15.6)	8 (25.0)	0.351
Smoker (active)	12 (37.5)	7 (21.9)	0.391
Family History			
Previous CVA	2 (6.2)	2 (6.2)	1.000
Previous MI	6 (18.8)	12 (37.5)	0.095
Previous PCI	5 (15.6)	9 (28.1)	0.226
Previous CABG	0	0	

Table 1 Baseline clinical and angiographic characteristics (*continued*)

	BRS (N=32)	MPS (N=32)	p value
Clinical presentation			
Stable or silent angina	10 (31.3)	18 (56.3)	0.074
Unstable angina	1 (3.1)	4 (12.5)	0.355
STEMI	4 (12.5)	0	0.155
NSTEMI	17(53.1)	9 (28.1)	0.074
Other	0	1 (3.1)	1.000
Target vessel			0.857
LAD	15 (46.9)	13 (40.6)	
LCX	6 (18.8)	6 (18.8)	
RCA	11 (34.4)	13 (40.6)	
RVD (mm)	2.90 (2.49, 3.18)	2.91 (2.29, 3.26)	0.803
MLD (mm)	0.92 (0.77, 1.57)	1.20 (0.75, 1.55)	0.453
Diameter stenosis (%)	60.00 (47.25, 72.75)	56.00 (46.00, 76.75)	0.452
Bifurcation	12 (37.5)	7 (21.9)	0.274
AHA Type			0.149
A	2 (6.3)	0	
B1	19 (59.4)	14 (43.8)	
B2	6 (18.8)	13 (40.6)	
C	5 (15.6)	5 (15.6)	
Calcification			
Mild	19 (59.4)	12 (37.5)	
Moderate/ severe	13 (40.6)	20 (62.5)	
Pre-treatment region length (mm)	22.19 (17.67, 25.08)	20.38 (17.05, 25.75)	0.803
Procedural details			
Pre-dilatation performed	29	18	0.004
Pre-dilatation balloon diameter	2.50 (2.50, 2.50)	2.00 (2.00; 2.50)	0.03
Post-dilatation	18	13	0.317
Post-dilatation diameter	3.00 (2.94; 3.50)	3.50 (2.75; 4.00)	0.253

Values are presented as number (%) or median (interquartile range)
AMI acute myocardial infarct; *BRS* bioresorbable scaffold; *CABG* coronary artery bypass graft; *CVA* cerebrovascular accident; *LAD* left anterior descending artery; *LCX* left circumflex artery; *MLD* minimal luminal diameter; *MPS* metallic platform stent; *PCI* percutaneous coronary intervention; *RCA* right coronary artery; *RVD* reference vessel diameter, *STEMI* ST-elevation myocardial infarct.

The left anterior descending artery was the most commonly treated vessel in the study population. Lesion calcification and complexity were similar between the two groups (Table 1). Procedural data are as shown in Table 1. Lesions treated with BRS were pre-dilatated more frequently and at higher pressures compared to the lesions treated with metallic stents. Pos-tdilatation rates were similar. The pre-treatment region length

was 21.38mm (17.67- 25.58) in the overall group. There were no significant differences in reference vessel diameter, minimal lumen diameter and percentage diameter stenosis in both groups. Pre-treatment curvature was similar between the BRS and MPS groups in both systole and diastole phases [systole: 0.290 (0.155-0.639) cm^{-1} vs 0.283 (0.125-0.519) respectively, p =0.803 and diastole: 0.305 (0.193- 0.580) cm^{-1} vs 0.257 (0.151-0.518) cm^{-1} respectively, p= 0.803].

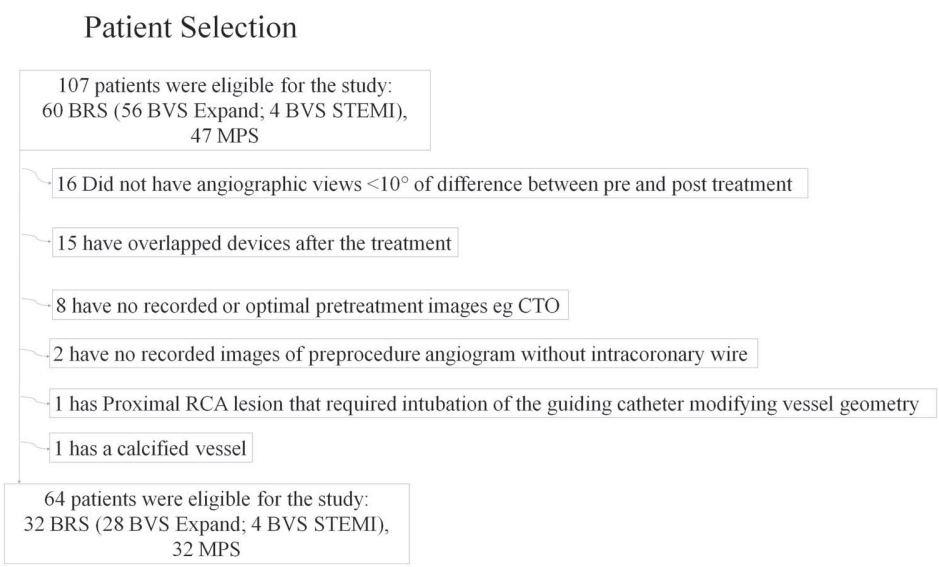

Figure 3 Flow chart of patient selection.
BRS bioresorbable scaffold, *CTO* chronic total occlusion, *MPS* metallic platform stents, *STEMI* ST elevation myocardial infarct

Geometric changes within and between groups

Table 2 shows the changes in curvature in both systole and diastole of the treated vessel in the BRS and MPS groups. After implantation of MPS, there was a significant decrease in median diastolic curvature (from 0.257 cm^{-1} to 0.199 cm^{-1}, p= 0.001) and median systolic curvature (0.283 cm^{-1} to 0.194 cm^{-1}, p <0.001) representing a percentage reduction of 16.0% and 28.6% respectively. Following an Absorb scaffold implantation, there was a trend towards a decrease in the median diastolic curvature (from 0.305 cm^{-1} to 0.283 cm^{-1}, p= 0.056) and median systolic curvature (from 0.290 cm^{-1} to 0.282 cm^{-1}, p= 0.061) which trends towards significance. As a result, the diastolic curvature was significantly higher in the BRS compared with the MPS group post treatment [BRS vs MPS; 0.283 cm^{-1} (0.150-0.541) vs 0.199 cm^{-1} (0.089-0.357), p= 0.035] (Figure 4). Post treatment, Percentage relative reduction in curvature was also smaller in the BRS group compared with MPS group in both the diastole and systole phases [BRS vs MPS; 7.48% vs 29.4%, p=

0.013; 9.04% vs 28.2%, p= 0.010 respectively]. Cyclic changes in curvature (i.e., between systole and diastole) were similar between the BRS than the MPS after the deployment in curvature (p = 0.271).

Table 2 Changes in curvature of the study population

		BRS (N=32)	MPS (N=32)	p value
Pre-treatment curvature(cm^{-1})				
	Systole	0.290 (0.155, 0.639)	0.283 (0.125, 0.519)	0.648
	Diastole	0.305 (0.193, 0.580)	0.257 (0.151, 0.518)	0.460
Post-treatment curvature(cm^{-1})				
	Systole	0.282 (0.147, 0.549)	0.194 (0.097, 0.407)	0.077
	Diastole	0.283 (0.150, 0.541)	0.199 (0.089, 0.357)	0.035
Percentage reduction in curvature post-pre-treatment [a]				
	Systole	2.76	28.6	
	Diastole	7.21	16.0	
Absolute reduction in curvature (cm^{-1})				
	Systole	0.024 (0.015, 0.087)	0.064 (0.010, 0.230)	0.034
	Diastole	0.021 (0.025, 0.098)	0.090 (0.011, 0.192)	0.066
Percentage relative change in curvature (cm^{-1})				
	Systole	-9.035(-22.128, 7.911)	-28.17 (-46.22, -6.64)	0.010
	Diastole	-7.484(-23.193, 8.355)	-29.43 (-50.31, -3.55)	0.013
Pre-treatment cyclic change in curvature (cm^{-1})		-0.021 (-0.072, 0.061)	0.002 (-0.086, 0.096)	0.398
Post-treatment cyclic change in curvature (cm^{-1})		-0.026(-0.054, 0.023)	-0.041 (-0.04, 0.125)	0.271

Values are presented as numbers or median (interquartile range).
[a] For BRS, the p values for comparison between pre and post curvature for systole and diastole are 0.061 and 0.056 respectively. For MPS, the p values for comparison between pre- and post-curvature for systole and diastole are <0.001(*) and 0.001(*) respectively
BRS bioresorbable scaffold; *MP*- Metallic platform stent

Predictive factors of modifying curvature

In univariate analysis, the use of MPS predicts a greater reduction in curvature with a coefficient of 23.33 (95% confidence interval: 3.81- 42.85, p = 0.02).

DISCUSSION

In summary, the major finding of this study showed that in the deployment of long coronary devices (28mm in length), BRS showed a non-significant decrease in curvature in

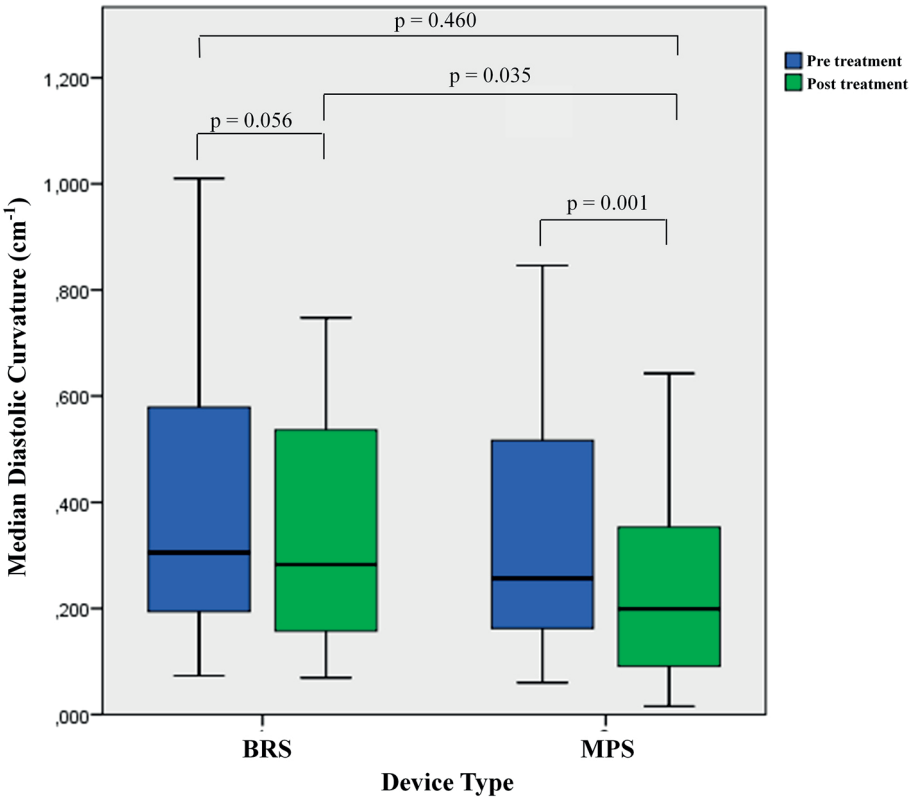

Figure 4 Change in curvature post treatment in BRS and MPS.
This boxplot illustrates the difference in median diastolic curvature post treatment in the BRS compared to the MPS group

the post treated vessel compared with a significant reduction in curvature of the treated vessel with deployment of a MPS. Use of MPS was an independent predictor of vessel curvature change post deployment.

Stent conformability is dependent on both the material and design of the stent and differs between the commercial devices that are available [13-15]. An open cell stent design would have higher conformability compared to a closed cell design. The difference in curvature post treatment between BRS and MPS could be attributed to the difference in underlying material composition of the devices in that a polymeric bioresorbable scaffold has better conformability to vessel geometry compared to metallic stents. In a study evaluating the bending stiffness of the BRS compared to the MPS in-vitro, the maximum compressive load of a BRS from ABSORB COHORT B trial was significantly lower compared to the XIENCE^{R} stent which signifies better conformability of the BRS (Figure 5) [16]. This is despite the fact that the strut thickness of the ABSORB Cohort B stent is thicker than that of the XIENCE^{R} stent (strut thickness 152.4 µm vs 81.3 µm). A previous

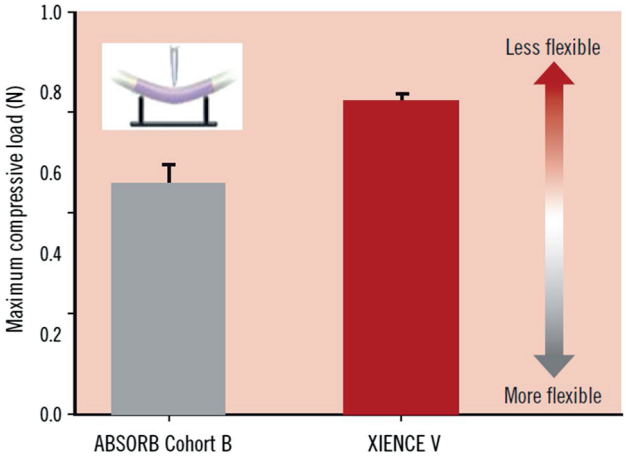

Figure 5 Maximum compressive force of ABSORB Cohort B scaffold and XIENCE V stent.
This figure shows the maximum compressive force applied to deflect the ABSORB Cohort B and XIENCE V 3.0×18 mm devices by 1.1 mm using 3 point- bend test (n=5). Statistical analysis yielded p=0.004 using One- way ANOVA and Tukey- Kramer HSD. Tests were performed by and data are on file at Abbott Vascular. (Reprinted from EuroIntervention Supplement (2009) Vol.5 Supplement F; Oberhauser JP, Hossainy S, Rapoza RJ. Design principles and performance of bioresorbable polymeric vascular scaffolds. F15-22, Copyright, with permission from Europa Digital and Publishing)

study had shown that the use of relatively shorter (18mm) BRS and MPS devices modify baseline vessel curvature but the change was more marked in the MPS compared with the BRS [7]. In this study, the median pre-treatment lesion length was 16.3 mm and 16.8 mm in the BRS and MPS groups respectively which are comparatively shorter compared to our study population. To our knowledge, this is the first in vivo study that shown that BRS does not affect the curvature of the treated vessel significantly in the deployment of long scaffolds. This might be of useful significance as we treat longer lesions with overlap scaffold required.

Though OCT has been widely described in existing methodology [17-20] to evaluate scaffold performance, OCT by itself is not able to measure curvature of the vessel, whereas QCA is available pre and post in almost all patients. From fluid dynamics and the resulting shear stress we know curvatures do have an impact on plaque formation in the following years where it is important to minimize the distortion of the natural vessel course post stent or scaffold implantation. As vascular geometry is the most important determinant of local wall shear stress, any beneficial effect on the conformability of the blood vessel might have clinical implications. Studies have demonstrated that low wall shear stress promotes atherosclerosis and plaque progression in native arteries [21] and greater intimal hyperplasia after stent deployment [22]. Metallic stents deployed in curved porcine coronary arteries were noted to cause vessel straightening in the stented segment and increased curvature at the stent edges [3]. A study by Gyongyosi et al had

further showed that a longitudinal straightening of stents is an additional predictor of major adverse events [23]. There are possible physiological and clinical benefits arising from the improvement in conformability in the bioresorbable scaffolds. An increased conformability of the BRS platform may result in physiological wall shear stress at the stent edges due to less vessel distortion. This may translate to clinical benefits such as reduced risk of scaffold edge restenosis. However, the clinical benefits associated with better conformability still needs further evaluation. This has become more relevant in the setting of recent data that showed a potential lack of benefits up to 3 years [24] particular certain lesion subsets such as smaller vessels with the BRS compared with best in class DES, with the BRS showing either similar or increased risk of TLR and increased risks of scaffold thrombosis compared to DES [25, 26].

Stent flexibility (and conformability) is also one of the key determinants of stent fracture, a common cause of late stent failure. Hinge motion (i.e. rocking back and forth on a bend) was one of the factors that can increase the risk of stent strut fracture. Our results suggest that there is a subtle but certain cyclic change of curvature after device implantation in both groups. Although there is no difference between groups, one can speculate that this cyclic movement repeating greater than 86400 times a day (based on average heart rate of 60 beats per minute) can cause mechanical failure at the metallic struts. In a study looking at predictors of stent fracture, stent fracture was identified in 2.9% of 1339 lesions treated with the XIENCE^{R} stent in only 6-9 months after placement [27]. In that study, the three major determinants of stent fracture in order of importance were hinge motion, ostial location and tortuosity. Since the BRS is programmed to get dismantled in the due course of the bioresorption, this might cause fewer problems with BRS than with MPS.

The impact of procedural factors such as predilation on conformability is still unknown. Although lesion pre and post-dilatation may potentially impact on outcome by its impact on lesion expansion (concentricity, eccentricity, final MLD/MLA, remaining DS% and AS%), changes in curvature is ultimately mostly influenced by the remaining implanted material characteristics and the design of the stent/scaffold (Number of longitudinal connectors). In clinical practice this is manifested by the straightening of the vessel during balloon inflations and increase in vessel curvatures directly after balloon deflation.

LIMITATIONS

We acknowledge the following limitations. The study is non-randomized and population in each group is relatively small. 2D angiographic analysis may also not be the most optimal imaging modality to assess the geometry of coronary vessels. However

the differences between the pre and post treatment angiographic views were less than 10°, indicating that the analysis were mainly performed in the same angiographic view. In addition, the precise impact of subsequent procedural steps (predilation, stent implantation, post-dilatation) on vascular curvature could not be entirely captured due to the inherent retrospective nature of our study and there was no specific protocol for operators to include the necessary angiographic or cinefluroscopic projections. Potentially this issue is best addressed in a future prospective study with dedicated research protocol ensuring the angiographic projections are obtained at the procedural steps of predilation, stent implantation and post-dilatation.

CONCLUSION

In the deployment of long coronary scaffolds/ stents (28mm in length), bioresorbable vascular scaffolds provides better conformability compared with MPS. The findings of this study and its clinical significance merits further evaluation.

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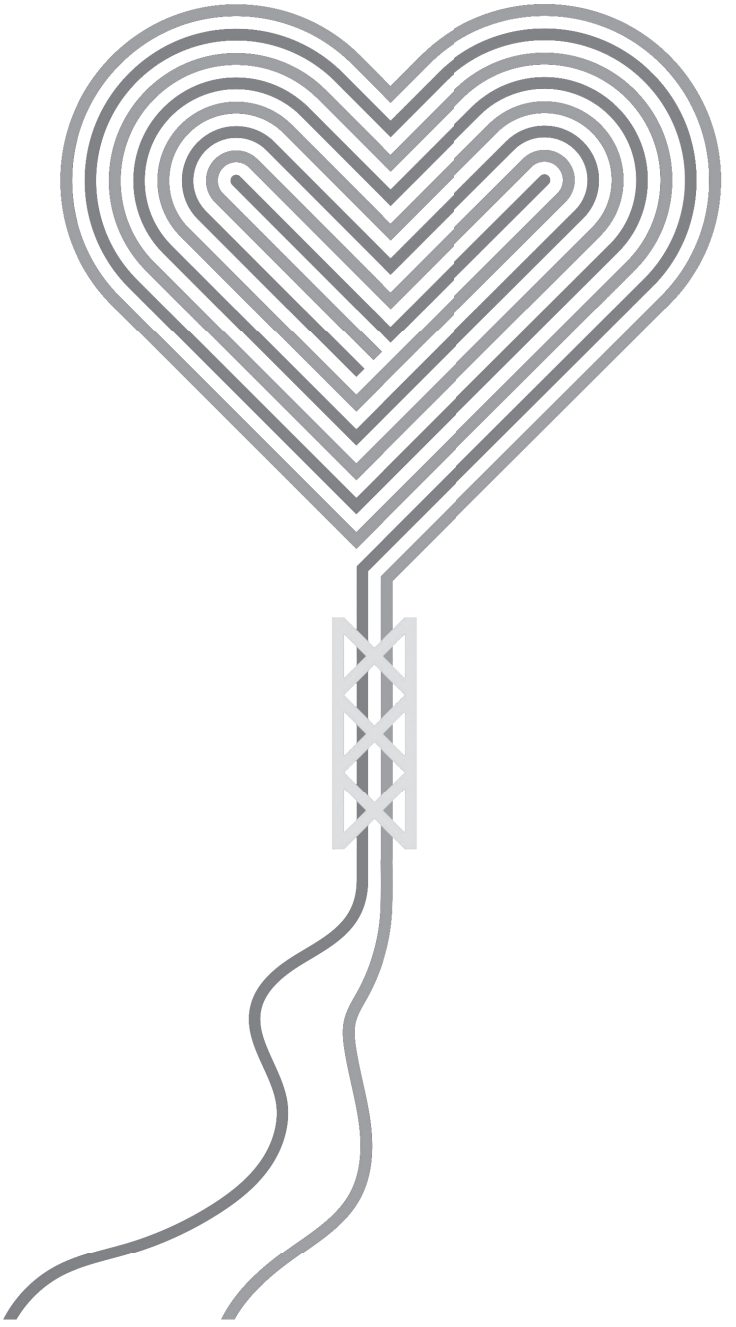

Part II

Clinical outcomes in higher risk patients and lesions

Chapter 5

Mid- to long-term clinical outcomes of patients treated with the everolimus-eluting bioresorbable vascular scaffold. The BVS Expand Registry

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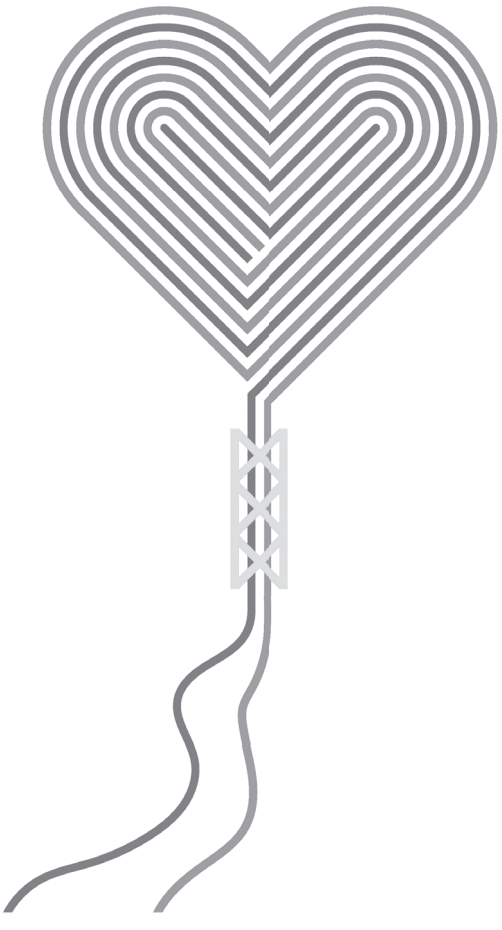

ABSTRACT

Objectives

To report on clinical outcomes beyond one year of the BVS Expand registry.

Background

Multiple studies have proven feasibility and safety of the Absorb bioresorbable vascular scaffold (BVS). However, data on medium to long-term outcomes are limited and available only for simpler lesions.

Methods

This is an investigator-initiated, prospective, single-center, single-arm study evaluating performance of the BVS in a lesion subset representative of daily clinical practice, including calcified lesions, total occlusions, long lesions and small vessels. Inclusion criteria were patients presenting with NSTEMI, stable/ unstable angina, or silent ischemia caused by a *de novo* stenotic lesion in a native previously untreated coronary artery. Procedural and medium to long-term clinical outcomes were assessed. Primary endpoint was major adverse cardiac events, defined as a composite of cardiac death, myocardial infarction and target lesion revascularization.

Results

From September 2012 to January 2015, 249 patients with 335 lesions were enrolled. Mean number of scaffolds per patient was 1.79±1.15. Invasive imaging was used in 39%. In 38.1% there were ACC/ AHA classification type B2/ C lesions. Mean lesion length was 22.16±13.79 mm. Post-procedural acute lumen gain was 1.39±0.59 mm. Median follow-up period was 622 days (interquartile range: 376-734). Using Kaplan-Meier methods, the MACE rate at 18 months was 6.8%. Rate of cardiac mortality, myocardial infarction and target lesion revascularization at 18 months were 1.8%, 5.2% and 4.0% respectively. Definite scaffold thrombosis rate was 1.9%.

Conclusions

In our study, BVS implantation in a complex patient and lesion subset was associated with an acceptable rate of adverse events at longer-term, while no cases of early thrombosis were observed.

INTRODUCTION

Drug-eluting stents (DES) currently form the mainstay of coronary devices used in percutaneous coronary interventions (PCI) in many parts of the world. Despite advantages in clinical outcomes such as reduction in target lesion revascularization rates, shortcomings related to the use of DES still exist such as delayed arterial healing, late stent thrombosis (ST) and hypersensitivity reactions to the polymer, with observations of ongoing very late stent failure beyond one year. [1, 2]

In addition, from a physiological point of view, a vessel that is indefinitely caged in a metal stent may not be desirable with both short- and long-term implications and potentially adverse consequences such as impaired endothelial function, the reduced potential for vessel remodelling, interference with the normal arterial healing process and the risk of occlusion of covered side branches by neointima hyperplasia. Furthermore, interference with non-invasive imaging (cardiac computed tomography or magnetic resonance imaging) during patient follow-up and possible impairment of future treatment options (re-PCI or coronary artery bypass surgery) are drawbacks of metallic stents. [3]

To overcome these issues, bioresorbable vascular scaffolds (BRS) were developed. The BRS most studied is the Absorb BVS (Abbott Vascular, Santa Clara, CA). The BVS provides transient vessel support and gradually elutes the anti-proliferative drug everolimus. After degradation of the polymer (after approximately three years) no foreign material remains and the risk for developing very late ST is potentially reduced.

Intravascular imaging observations 5 years after BVS implantation in a simple patient and lesion subset have demonstrated late luminal enlargement due to plaque reduction, a persistent restoration of vasomotion and a fully completed bioresorption process, [4, 5] and a low rate of major adverse cardiac events (MACE) rate (3.4%). [6] This is consistent in randomized controlled trials (ABSORB II and ABSORB Japan) which showed comparable clinical event rates in BVS compared with best in class with metallic DES (Xience V). [7, 8] However, as these studies included a selected group of patients, extrapolation to a more complex population is limited. Yet, the registry- level clinical data on the outcomes after BVS implantation in more complex patient and lesion subsets have not been well documented that such data are available from registries with a relatively short follow-up of 6 to 12 months, which have shown variable early clinical outcomes. [8-10] Thus, the medium to long-term outcomes beyond one year after BVS implantation in such complex 'real-world' lesions remain elusive.

In the current study, we report on extended follow-up beyond one year, of the BVS Expand Registry. This is a single-center registry initiated in September 2012 that investigates the clinical outcomes after BVS implantation in a more complex real-world population.

METHODS

Population

This is an investigator-initiated, prospective, single-center, single-arm study performed in an experienced, tertiary PCI center. Patients presenting with NSTEMI, stable or unstable angina (UA), or silent ischemia caused by a *de novo* stenotic lesion in a native previously untreated coronary artery with intention to treat with a BVS were included. Angiographic inclusion criteria included lesions with a Dmax (proximal and distal maximal lumen diameter) within the upper limit of 3.8 mm and the lower limit of 2.0 mm by online quantitative coronary angiography (QCA). Complex lesions such as bifurcation, calcified (as assessed by angiography), long and thrombotic lesions were not excluded. Exclusion criteria were patients with a history of coronary bypass grafting (CABG), presentation with cardiogenic shock, bifurcation lesions requiring kissing balloon post-dilatation, ST-elevation myocardial infarction (STEMI) patients, allergy or contra-indications to antiplatelet therapy, fertile female patients not taking adequate contraceptives or currently breastfeeding and patients with expected survival of less than one year. As per hospital policy patients with a previously implanted metal DES in the intended target vessel were also excluded. Also, although old age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age.

Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC, and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. Approval of the ethical board of the Erasmus MC was obtained. All patients undergoing clinical follow-up provided written informed consent for the PCI and to be contacted regularly during the follow-up period of the study.

Procedure

PCI was performed according to current clinical practice standards. The radial or femoral routes were the principal routes of vascular access and 6 or 7 French catheters were used depending on the discretion of the operator. Pre-dilatation and post dilation were recommended with a balloon shorter than the planned study device length and with a non-compliant balloon without overexpanding the scaffold beyond its limits of expansion (0.5mm > nominal diameter) respectively. Intravascular imaging with the use of Intravascular Ultrasound (IVUS) or Optical Coherence Tomography (OCT) was used for pre-procedural sizing and optimization of stent deployment on the discretion of the operator. All patients were treated with unfractionated heparin (at a dose of 70-100 UI/kg). Patients with stable angina were preloaded with 300 mg of aspirin and 600 mg of

clopidogrel. Patients presenting with ACS were preloaded with 300 mg of aspirin and 60 mg of prasugrel or 180 mg of ticagrelor.

Angiographic analysis

Quantitative Coronary Analysis (QCA) was performed by three independent investigators. Coronary angiograms were analyzed with the CAAS 5.10 QCA software (Pie Medical BV, Maastricht, the Netherlands). The QCA measurements provided reference vessel diameter (RVD), percentage diameter stenosis, minimal lumen diameter (MLD), and maximal lumen diameter (Dmax). Acute gain was defined as post-procedural MLD minus pre-procedural MLD (in an occluded vessel MLD value was zero by default). For the purpose of this study we defined underexpansion as a ratio of post-procedural minimal lumen diameter (MLD) to the nominal device diameter of less than 0.7. The ratio of pre-procedural reference vessel diameter (RVD) to the nominal device diameter was used to assess pre-procedural sizing.

Follow-up

Clinical demographic data of all patients were obtained from municipal civil registries. Follow-up information specific for hospitalization and cardiovascular events was obtained through questionnaires. If needed, medical records or discharge letters from other hospitals were requested. Events were adjudicated by an independent clinical events committee (CEC). All information concerning baseline characteristics and follow-up was gathered in a clinical data management system.

Definitions

The primary endpoint was MACE, defined as the composite endpoint of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). Deaths were considered cardiac unless a non-cardiac cause was definitely identified. TLR was described as any repeated revascularization of the target lesion. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Non-target vessel revascularization was described as any revascularization in a vessel other than the target lesion. Scaffold thrombosis (ST) and MI were classified according to the Academic Research Consortium (ARC). [11] Clinical device success (lesion basis) was defined as successful delivery and deployment of all intended scaffolds at the target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold residual stenosis of < 30% as evaluated by QCA. When bailout device was used, the success or failure of the bailout device delivery and deployment is not one of the criteria for device success. Clinical procedure success (patient basis) was described as achievement of final in-scaffold residual stenosis of less than 30% by QCA with successful delivery and deployment of all intended scaffolds at

the target lesion and successful withdrawal of the delivery system for all target lesions without major peri-procedural complications or in-hospital MACE (maximum of 7 days). In dual target lesion setting, both lesions must meet clinical procedure success criteria to have a patient level procedure success.

The intention-to-treat (ITT) group includes all the patients regardless of whether or not the scaffold was successfully implanted. The per-treatment (PT) group consists of all patients in whom the BVS was successfully implanted. Only events in the per-treatment population were analysed.

The off-registry population consisted of patients that were excluded in this study, mainly STEMI patients.

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. The student's t test and the chi square test (or Fishers' exact test) were used for comparison of means and percentages. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical tests were two-sided and the P value of < 0.05 was considered statistically significant. To investigate possible predictors for clinical outcomes MACE and ST, univariate analysis using a Cox regression model was used investigating variables that are frequently present. Statistical analyses were performed using SPSS, version 21 (IL, US).

RESULTS

From September 2012 up to January 2015, 3373 patients were treated with PCI in our center. The majority of patients were considered not suitable for BVS either to their biological age related to comorbidities, indication for stent > 3.5mm or smaller < 2.5 mm, previous CABG, previous PCI with metal DES in the target vessel or STEMI as indication for PCI shortly after the commercial introduction of BVS in Europe. These patients were in general older (64.5 ± 11.6 years) and presented with more risk factors compared to the BVS population (previous CABG: 9.5%, previous PCI: 31.3%, previous MI: 25.6%) and presented more frequently with multivessel disease (57.8%). Finally, 485 patients were treated with one or more BVS in the registry period. Most excluded patients (N = 169) presented with STEMI and entered a separate registry starting later, 5 had a previous CABG, 1 needed kissing balloon post-dilatation for bifurcation, 2 had a previous implanted metal DES in the target vessel as formal exclusion criteria for this analysis and

58 patients did not return their informed consent because they declined to participate, emigrated abroad or participated in another trial investigating BVS.

249 signed the informed consent for follow-up and were eligible based on protocol inclusion and exclusion criteria. In 5 patients delivery failure occurred (intention-to-treat, ITT group). The per-treatment (PT) group thus consisted of 244 patients. The flowchart of the registry is given in Figure 1.

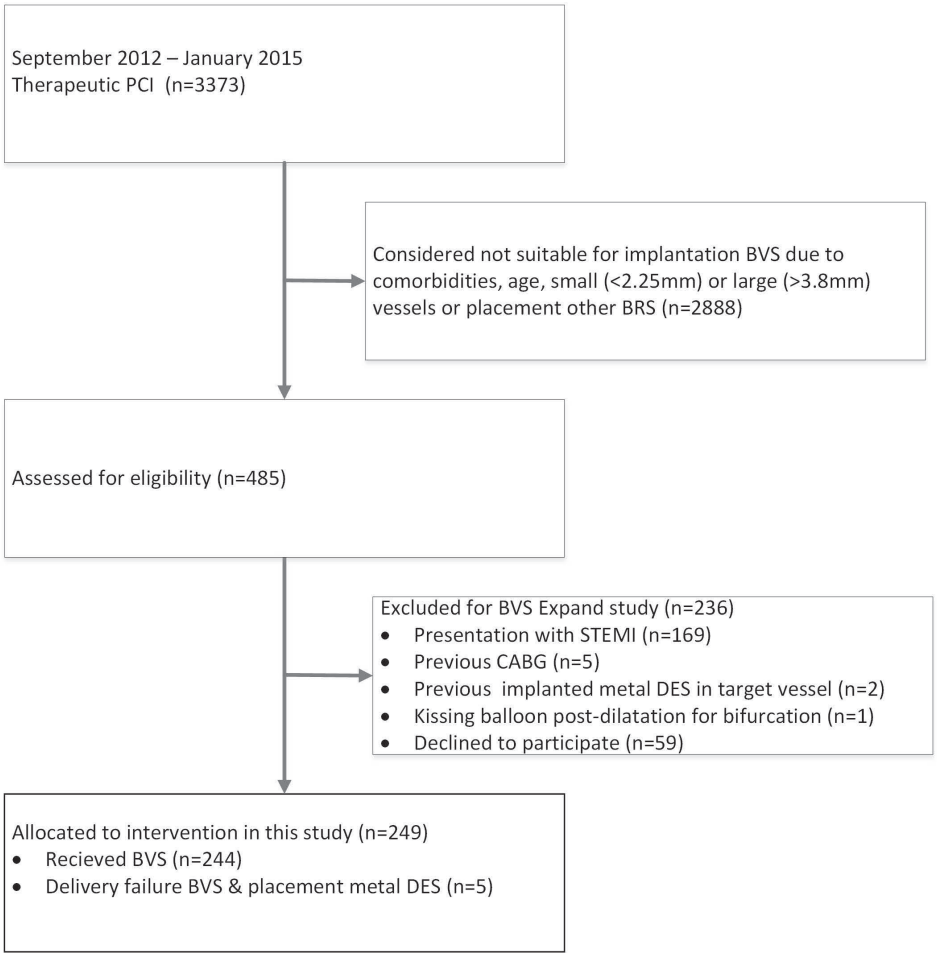

Figure 1 Flowchart of the study

Baseline characteristics

Baseline characteristics of all BVS treated patients are presented in Table 1. Mean age was 61.3 ± 10.2 years, 73.5% were male, 18.5% diabetic and 59.1% presented with an acute coronary syndrome (NSTEMI or UA; STEMI patients were excluded). Multivessel disease

was present in 45.6%. The off-registry patients were younger, with less comorbidities and presented more frequently with STEMI.

Table 1 Baseline characteristics

Patients characteristics	ITT population	Off-registry population	P value
Number of patients	249	236	
Gender (%)			0.57
Men	73.5	75.6	
Women	26.5	24.4	
Mean age in years (±SD)	61.3 ± 10.2	55.4 ± 10.6	P<0.001
Smoking (%)	55.0	59.0	0.24
Hypertension (%)	59.4	41.9	P<0.001
Dyslipidaemia (%)	51.0	29.9	P<0.001
Diabetes Mellitus (%)	18.5	13.2	0.14
Family history of CAD (%)	44.6	37.6	0.23
Prior MI (%)	17.7	6.0	P<0.001
Prior PCI (%)	9.2	4.7	0.05
Prior CABG (%)	0.0	2.6	0.01
Presenting with multiple vessel disease (%)	45.6	28.2	0.07
Indication for PCI (%)			P<0.001
Stable angina	40.6	9.8	
Unstable angina	16.1	2.1	
STEMI	0.0	71.4	
NSTEMI	43.0	16.7	
Silent ischemia	0.4	0.0	
Periphery artery disease (%)	8.8	1.7	P<0.001
COPD (%)	7.2	3.9	0.10
Heart failure (%)	4.8	0.9	0.01
Renal insufficiency (%)	6.4	2.1	0.02
CVA/ TIA (%)	9.6	4.3	0.03

CAD coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CVA* cerebrovascular accident, *TIA* transient ischemic attack

Lesion characteristics are presented in table 2. The left anterior descending coronary artery (LAD) was most commonly treated (50.0% of lesions). Moderate or severe calcification (as assessed by angiography) was present in 42.2% and a chronic total occlusion in 4.2% of the lesions. Bifurcation lesions (involving lesions within 3 mm of the bifurcation and with side branches ≥ 2 mm by visual estimation in diameter, treated with implantation of at least one BVS) were present in 21.3% with significant side branch involvement (true bifurcations: Medina 1,1,1, 1,0,1 and 0,1,1 lesions) in 32% of these. Overall, 38.1%

Table 2 Lesion characteristics

		N= 249; L= 335
Target vessel (%)		
	LAD	50.0
	LCX	23.7
	RCA	26.0
	Ramus intermedius	0.3
	SVG	0.0
Lesion AHA A/B1/B2/C		16.2/ 45.8/ 24.3/ 13.8
Bifurcation (%)		21.3
Moderate/ severe calcification (%)		42.2
(Chronic) Total occlusions (%)		4.2
TIMI (%)		
Pre-procedure		
	TIMI 0	8.4
	TIMI 1	1.8
	TIMI 2	13.8
	TIMI 3	75.4
Post-procedure		
	TIMI 0	0.0
	TIMI 1	0.3
	TIMI 2	3.0
	TIMI 3	96.4
QCA Analysis		
Pre-procedure		
	Lesion length (mm)	22.10 ± 13.90
	RVD (mm)	2.42 ± 0.74
	MLD (mm)	0.91 ± 0.45
	Diameter stenosis (%)	59.13 ± 20.72
Post-procedure		
	RVD (mm)	2.77 ± 0.46
	MLD (mm)	2.30 ± 0.42
	Diameter stenosis (%)	16.90 ± 9.04
	Acute lumen gain (mm)	1.39 ± 0.59

Values are expressed as percentages or mean ± standard deviation when appropriate. *LAD* left anterior descending artery, *LCX* left coronary artery, *MLD* minimal lumen diameter, *QCA* quantitative coronary angiography, *RCA* right coronary artery, *RVD* reference vessel diameter, *SVG* saphenous vein graft

of lesions were ACC/ AHA type B2 or C. Mean lesion length was 22.16 ± 13.79 mm. Pre-procedural QCA showed a RVD of 2.42 ± 0.74 mm, a MLD of 0.91 ± 0.45 mm and a %DS of 59.12 ± 20.72%.

Procedural details

Table 3 shows the procedural characteristics. Pre-dilatation was performed in 89.9% (pre-dilatation balloon to artery ratio of 1.05 ± 0.23). Post-dilatation was performed in 53.3% with a balloon to scaffold ratio of 1.08 ± 0.11. Advanced lesion preparation using rotational artherectomy and scoring balloon was done in 3.1% and 2.7%. Pre-procedural evaluation and device optimization using invasive imaging with IVUS and OCT was done in 14.4% and 24.6% of the procedures, respectively. A total of 445 BVS were implanted with a mean number of 1.34 ± 0.69 scaffolds per lesion and a mean number of 1.79 ± 1.15 scaffolds per patient. For the bifurcation lesions, the provisional side branch treatment was standard in this study. Side branch wiring before main vessel stenting was employed in 37.5%. Side branch dilation after main vessel stent was performed for 31% and bailout stenting only in one BVS. Side branch fenestration was performed in 25%. Side branch dilation was followed by mini-kissing post-dilation of just sequential ballooning with proximal optimization.

Post-procedural QCA characteristics were: RVD 2.77 ± 0.46 mm, MLD 2.30 ± 0.42 mm and %DS 16.90 ± 9.04. Acute lumen gain was 1.39 ± 0.59 mm.

Clinical device success was 97.3% and clinical procedural success was 96.8%. In 5 patients delivery failure of the BVS occurred because the scaffold could not pass the lesion, for example due to severe calcification or tortuosity. After multiple attempts, metal DES were placed in these cases.

Clinical outcomes

Survival data was available in 100% with a median follow-up period of 622 days (interquartile range [IQR], 376-734 days). Two patients withdrew their informed consent within a few weeks after the index procedure.

One-year clinical outcomes are reported in Table 4. Event rates are described as Kaplan-Meier estimates. Figures 2A – 2C give an impression of the event rates during late follow-up. At 18 months, there were 4 fatalities (all cardiac death) with a Kaplan-Meier estimate of 1.8%. In the per-treatment group, MACE rate at 18 months was 6.8%, mainly driven by the rate of MI (5.2%). There were two cases of peri-procedural MI. TLR at 18 months was performed in 4.0%, TVR in 4.0%. Rate of non-TVR was 5.4%. Rate of overall ST at 18 months was 2.7%, with a definite ST rate of 1.9%.

Details of ST cases are summarized in Table 5. Narratives of each case are presented in the supplemental material. In Figure 3 we present MACE, its components and definite/ probable ST rates in various subgroups. There was no increased rate of both MACE and definite/ probable ST in patients presenting with ACS (NSTEMI and unstable angina) compared to the overall population.

Bar graphs demonstrating the rate of major adverse cardiac event (MACE) rate, its components, and scaffold thrombosis in subgroups of population (e.g. calcification, bifurcation, small vessel). *MI* myocardial infarction, *NS* non-ST-segment elevation

Table 3 Procedural characteristics

		N= 249; L= 335
Treated lesion per procedure		1.35 ± 0.62
Aspiration thrombectomy (%)		4.2
Rotablation (%)		3.1
Scoring balloon (%)		2.7
Intracoronary imaging (%)		
	IVUS	14.4
	OCT	24.6
Pre-dilation (%)		89.8
Max pre-dilation diameter (mm)		2.61 ± 0.44
Pre-dilation balloon: artery ratio		1.05 ± 0.23
Maximum pre-dilation inflation pressure (atm)		12.80 ± 5.91
Buddy wire (%)		8.1
Mean number of scaffolds/ lesion		1.34 ± 0.69
Mean number of scaffolds/ patient		1.79 ± 1.15
Number of scaffolds		445
	1 (%)	72.6
	2 (%)	20.3
	3 (%)	4.5
	4 (%)	2.5
Scaffold diameter (mm)		3.08 ± 0.35
Scaffold length implanted (mm)		28.31 ± 17.06
Lesions with Overlapping scaffolds (%)		25.4
Overlap scaffolds diameters 3.5 mm–3.5 mm (%)		24
Overlap scaffolds diameters 3.5 mm–3.0 mm		23
Overlap scaffolds diameters 3.5 mm–2.5 mm		7
Overlap scaffolds diameters 3.0 mm–3.0 mm		21
Overlap scaffolds diameters 3.0 mm–2.5 mm		29
Overlap scaffolds diameters 2.5 mm–2.5 mm		11
Maximum scaffold implantation pressure (atm)		15.08 ± 1.82
Post-dilation (%)		53.3
Post-dilation balloon: mean scaffold diameter ratio		1.08 ± 0.11
Max post-dilation balloon (mm)		3.20 ± 0.46
Maximum post-dilation inflation pressure (atm)		15.50 ± 3.42
Procedural complications (%)		
	Dissection	5.1
	Slow flow/ no reflow	2.7
Clinical device success (%)		97.3
Clinical procedural success (%)		96.8

Values are expressed as percentages or mean ± standard deviation when appropriate.

Table 4 Kaplan-Meier estimates at one-year for clinical events rates

Clinical event rates at one year		ITT (N=249)	PT (N=244)
MACE (%)		5.5	5.1
All cause death (%)		1.3	1.3
	Cardiac death	1.3	1.3
	Non-cardiac death	0.0	0.0
All myocardial infarction (%)*		3.8	3.4
	Target-vessel	2.8	2.5
Target lesion revascularization (%)		3.8	3.4
Target vessel revascularization (%)		3.8	3.4
Non-target vessel revascularization (%)		3.9	3.7
Total scaffold thrombosis (%)		2.1	2.1
Definite scaffold thrombosis (%)		1.3	1.3
	Acute	0.0	0.0
	Subacute	0.0	0.0
	Late	1.3	1.3
Probable scaffold thrombosis (%)		0.4	0.4
	Acute	0.0	0.0
	Subacute	0.0	0.0
	Late	0.4	0.4
Possible scaffold thrombosis (%)		0.4	0.4
	Acute	0.0	0.0
	Subacute	0.0	0.0
	Late	0.4	0.4
Bleeding (Gusto) (%)		2.1	2.2
CVA/ TIA (%)		0.9	0.9

CVA cerebrovascular accident, *ITT* intention-to-treat, *MACE* major adverse cardiac events (composite end-point of cardiac death, myocardial infarction and target lesion revascularization), *PT* per-treatment, *TIA* transient ischemic attack

myocardial infarction, *ST* scaffold thrombosis, *TLR* target lesion revascularization, *UA* unstable angina

Univariate analysis was performed to identify predictors for the occurrence of MACE and definite/ probable ST (Table 6 and 7). Due to lack of power, none of the factors were significant. However, regarding MACE, the following characteristics tended to be associated with ≥ 2 times increased risk of MACE: male (HR 4.079, P = 0.18), more than 2 scaffolds/ lesion (HR 2.41, P = 0.19), underexpansion (HR 2.25, P = 0.16 and age > 65 years (HR 2.11, P = 0.20) (Table 6). Regarding ST, the following characteristics tended to be associated with ≥ 3 times increased risk of ST: age > 65 years (HR 4.49, P = 0.19), long

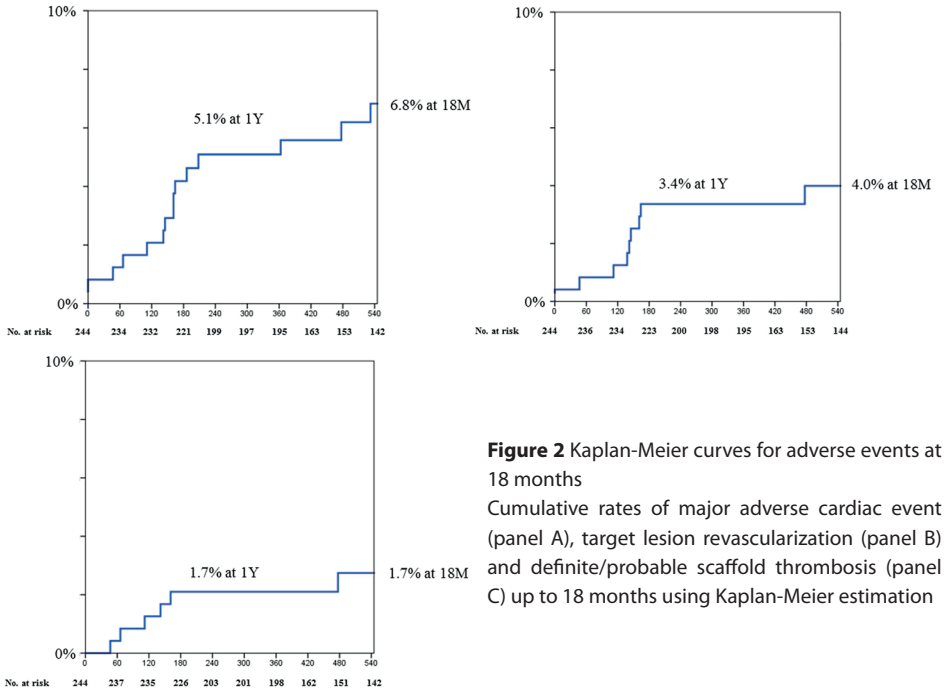

Figure 2 Kaplan-Meier curves for adverse events at 18 months
Cumulative rates of major adverse cardiac event (panel A), target lesion revascularization (panel B) and definite/probable scaffold thrombosis (panel C) up to 18 months using Kaplan-Meier estimation

lesions (HR 3.55, P = 0.27 for lesions of 20 mm and HR 3.42, P = 0.22 for lesions of 32 mm), calcified lesion (HR 3.55, P = 0.27) and RVD ≤ 2.5 mm (HR 3.26, P = 0.31).

Concerning intravascular imaging at baseline, patients who did not undergo baseline imaging had a TLR rate of 4.0%, compared to 2.3% in patients who did undergo baseline imaging (P Log Rank = 0.29). Intravascular imaging was performed more often in patients who had a complex lesion (AHA classification type B2/ C lesion): 44.5% vs 31.1%, P = 0.03.

To examine the relationship between underexpansion, sizing and MACE, a scatterplot of the pre-procedural sizing and post-procedural expansion divided by nominal diameter was created based on QCA (Figure 4). When a cut-off value of MLD post-procedure / nominal device diameter of < 0.70 is applied, the scaffold was underexpanded in 26% of the lesions. Patients, in whom underexpansion occurred, tended to have an increased rate of MACE: 8.0% versus 3.8% (P = 0.15, log rank test).

Table 5 Overview cases ST

Case	Time (d)	Type ST	Age (yr)	Presentation at baseline	Vessel	BVS	Pre-dil	Post-dil	Baseline imaging	Patient related factor	DAPT	Possible mechanism ST	Treatment during event
1	47	Def	69	NSTEMI	LAD	3.0x28, 3.5x18, 3.5x18	Yes	Yes	Yes	Yes (PCI for ACS)	Yes	Residual thrombus, total occlusion, long lesion, calcification, bifurcation	Thrombectomy, eptifibatide, Xience (3.5x38)
2	66	Poss	76	SAP	LAD	3.0x18	Yes	Yes	Yes	Yes (KD, SM)	Yes	Bifurcation, calcification	None, sudden death
3	112	Def	58	SAP	LAD	3.5x28	Yes	Yes	Yes	Yes (SM, ↓ LVF)	Yes	NIH, calcification, underexpansion, long lesion, small vessel	Thrombectomy, Promus (3.5x32), eptifibatide
4	142	Prob	65	NSTEMI	LAD	3.0x18	Yes	Yes	No	Yes (PCI for ACS, SM)	Yes	Geographical miss, edge restenosis, trifurcated lesion	Thrombectomy, Promus (3.5x38mm)
5	161	Def	70	Decreased LVF	LAD	2.5x18 3.0x18	Yes	Yes	Yes	Yes (KD, SM, ↓ LVF)	No	Interruption anticoagulants due to surgery, calcification, long lesion, small vessel	POBA, eptifibatide

DAPT dual antiplatelet therapy, *Def* definite, *DM* diabetes mellitus, *KD* kidney disease, *LVF* left ventricular function, *NSTEMI* non-ST elevation myocardial infarction, *POBA* plain old balloon angioplasty, *Poss* possible, *Post-dil* post-dilatation, *Pre-dil* pre-dilatation, *Prob* probable, *SAP*: stable angina pectoris, *SM* smoking, *ST* scaffold thrombosis

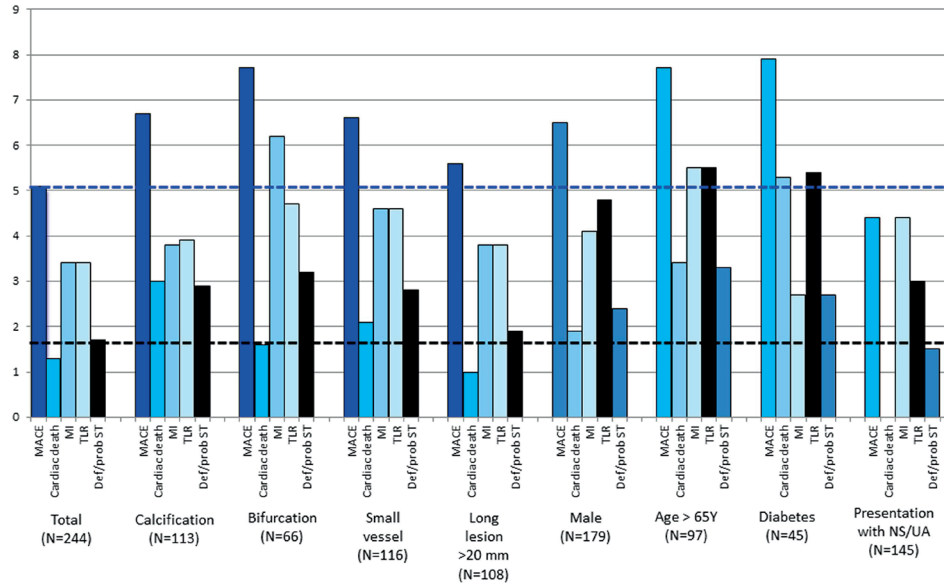

Figure 3 Rate of MACE and Definite/Probable ST, divided by subgroups
Bar graphs demonstrating the rate of major cardiac adverse event (MACE) rate, its components, and scaffold thrombosis in subgroups of population (e.g., calcification, bifurcation, small vessel). MI = myocardial infarction; NS = non-ST-segment elevation myocardial infarction; ST = scaffold thrombosis; TLR = target lesion revascularization; UA = unstable angina.

Table 6 Univariate analysis of MACE

	Hazard Ratio (95% confidence interval)	P value
Male	4.07 (0.53 – 31.51)	0.18
> 2 scaffolds/ lesion	2.41 (0.66 – 8.84)	0.19
Underexpansion	2.25 (0.73 – 6.98)	0.16
Age > 65 years	2.11 (0.67 – 6.64)	0.20
Bifurcation lesion	1.97 (0.63 – 6.21)	0.25
Long lesion (>32mm)	1.73 (0.52 – 5.76)	0.37
Long lesion (>20mm)	1.67 (0.53 – 5.27)	0.38
Calcified lesion	1.64 (0.52 – 5.17)	0.39
Overlap	1.59 (0.49 – 5.17)	0.44
RVD ≤ 2.5mm	1.56 (0.49 – 4.91)	0.45
Diabetes Mellitus	1.51 (0.41 – 5.57)	0.54
Presentation with ACS	0.71 (0.23 – 2.20)	0.55
Imaging at baseline	0.55 (0.15 – 2.03)	0.37

ACS acute coronary syndrome (NSTEMI and unstable angina pectoris), *MACE* major adverse cardiac events (composite endpoint of cardiac death, myocardial infarction and target lesion revascularization), *MLD* minimal lumen diameter, *RVD* reference vessel diameter (pre-procedural), *Underexpansion* (PostMLD/ nominal device diameter) < 0.7

Table 7 Univariate analysis of probable/ definite ST

	Hazard Ratio (95% confidence interval)	P value
Age > 65 years	4.49 (0.47 – 43.15)	0.19
Long lesion (>20mm)	3.55 (0.37 – 34.13)	0.27
Calcified lesion	3.55 (0.37 – 34.13)	0.27
Long lesion (>32mm)	3.42 (0.48 – 24.26)	0.22
RVD ≤ 2.5mm	3.26 (0.34 – 31.34)	0.31
Bifurcation lesion	2.72 (0.38 – 19.31)	0.32
Overlap	2.20 (0.30 – 15.92)	0.44
Underexpansion	2.19 (0.31 – 15.53)	0.43
> 2 scaffolds/ lesion	1.74 (0.21 – 14.70)	0.61
Diabetes Mellitus	1.52 (0.16 – 14.64)	0.72
Presentation with ACS	0.70 (0.10 – 4.96)	0.72

ACS acute coronary syndrome (NSTEMI and unstable angina pectoris), *MLD* minimal lumen diameter, *RVD* reference vessel diameter (pre-procedural), *ST* scaffold thrombosis, Underexpansion: (PostMLD/ nominal device diameter) < 0.7

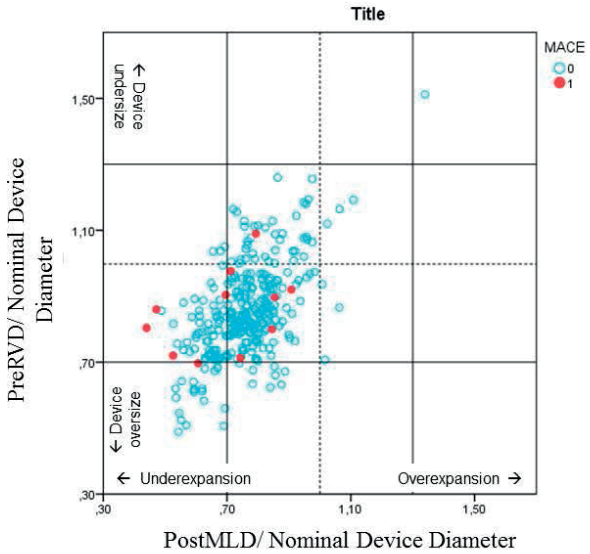

Figure 4 Relation of BVS underexpansion and MACE
BVS = bioresorbable vascular scaffold; MACE = major adverse cardiac events; MLD = minimal lumen diameter; RVD = reference vessel diameter.

DISCUSSION

To the best of our knowledge this is the first registry reporting on the extended follow-up beyond one year, with a median follow-up duration of 622 days. The main findings of our study are that: 1) 12-month MACE incidence for the per-treatment group was 5.1%, mainly driven by rate of MI (approximately 70% due to target vessel MI), with a further flattening of Kaplan-Meier after one year (6.8% at 18 months); 2) the rate of definite/probable ST at one year was 1.7% which is higher compared to second generation metal DES; [12] 3) patients with acute coronary syndrome did not have increased risk of MACE and ST; and 4) underexpansion of the BVS was a rather frequent finding and there was a trend for an increased rate of MACE.

The BVS Expand registry describes the procedural and medium to long-term clinical outcomes of BVS in patients with native, de novo coronary artery disease. Other studies investigating clinical outcomes of BVS were often characterized by small sample size and inclusion of patients with non-complex lesions. In this single-center study we report event rates in a more complex lesions including long lesions (mean lesion length 22.10 ± 13.90 mm), calcified and bifurcated lesions, with a relatively high proportion of ACC/AHA type B2 or C lesions (38.1%). Furthermore and different from other registries [10], all events were adjudicated by an independent CEC and all angiograms were analysed using QCA, creating a complete QCA database. Finally, in the present registry there were limited angiographic exclusion criteria that allowed a study population that is more reflective of a 'real-world' population.

Taking into account the complexity of the treated lesions, the one-year MACE rate of 5.1% observed in the current registry is low and in line with previous trials using BVS in relatively simple lesions: 5% in the ABSORB II trial [7], 5.0% in the ASSURE BVS registry [9], 4.3% in the BVS Extend trial. [13] Recently, several European registries reported on the 6-month clinical outcomes after implantation of BVS in all-comer settings (Table 8). In our registry, 6-month MACE rate was 4.7% which is comparable to the other registries.

Recently, some concerns were raised regarding a potentially increased rate of ST after implantation of the Absorb BVS. [10, 14, 15] Stent thrombosis in the case of metallic DES is an entity with complex multifactorial pathomechanisms, something that probably applies to the case of BVS. [16] The importance of patient selection, lesion preparation, pre- and post-dilatation and the consideration of invasive imaging for optimal device deployment have to be emphasized [17, 18], while DAPT (dual antiplatelet therapy) continuation for at least one year is recommended. Pilot imaging observations in real-world patients with BVS thrombosis suggest suboptimal implantation with underexpansion, malapposition, and incomplete lesion coverage, often in combination with DAPT discontinuation to be the major substrate both for acute and late events. [19] Although it is not clear why this complication is observed in high incidence with BVS, a potential explanation could

Table 8 Overview BVS Registries

	ABSORB A	ABSORB B	ABSORB II	BVS EXTEND	ASSURE	ABSORB FIRST	AMC	Milan	GHOST-EU	Robaei et al.	Polish National Registry	BVS EXPAND
N	30	101	355	512	183	800	135	92	1189	100	591	249
Sites	4	9	46	56	6	95	1	2	10	2	30	1
Period	03/06-07/06	03/09-11/09	11/11-06/13	1/10-12/12	4/12-3/13	1/13-3/14	8/12-8/13	5/12-8/13	11/11-1/14	12/10-10/13	10/12-11/13	9/12-01/15
ACS	27%	-	20%	0%	21.3%	38%	48.8%	10.9%	47.4%	44%	52%	59.1%
Single vessel PCI	100%	99%	-	93%	-	90.7%	81.1%	-	-	85%	-	76.7%
Lesions/ patient	1.0	1.0	1.0	1.1	1.1	1.2	1.2	1.5	1.2	1.5	-	1.4
Lesion length	8.2 mm	9.7 mm	21.1mm	11.9 mm	15 mm	18.3 mm	-	36.5 mm	19.4 mm	20.9mm	-	22.1 mm
Calcification	-	-	13%	15%	15.7%	20.4%	11.3%	20.4%	-	-	-	45.8%
B2	40%	53.5%	44.0%	41%	43.4%	23.1%	42.1%	83.9%	23.6%	19%	-	24.3%
C	0.0%	5.9%	2.0%	2%	21.2%	23.6%	25.2%		27.6%	37%	-	13.8%
Baseline Imaging	100% (IVUS documentary)	100% (IVUS, documentary)	100% (IVUS documentary)	-	-	-	25.0%	-	28.2%	15.8%	-	39.0%
Device success	94%	100%?	99.0%	98.6%	-	98.9%	96.0%	-	99.7%	98.8%	100%	97.3%
TLR	3.4% at 5 years	5.0%	1%	1.8% at 1 year	2.8% at 1 year	-	5.0% at 6 months	3.3% at 6 months	2.5% at 6 months	0%	-	3.1% at 1 year
TVR	10.3.% at 5 years	-	2%	-	-	-	6.6% at 6 months	3.3% at 6 months	4.0% at 6 months	0%	-	3.1% at 1 year
Definite scaffold thrombosis	0% at 5 years	0%	0.6%	0.8% at 1 year	0% at 1 year	0.3% at 30 days	3.2% at 6 months	0% at 6 months	1.7% at 6 months	0% at 30 days	-	1.3% at 1 year
Acute Def ST	0%	0%	0.3%	0.0%	0%	-	0.0%	0%	1.2% (def/ prob ST)	0%	-	0%
Subacute Def ST	0%	0%	0.3%	0.4%	0%	-	2.4%	0%	1.2% (def/ prob ST)	0%	-	0%
Late Def ST	0%	0%	0%	0.4%	0%	-	0.8%	0%	0.5%	0%	-	1.3%
MACE	3.4% at 5 years	9.9% at 3 years	5.0% at 1 year	4.3% at 1 year	5% at 1 year	-	-	3.3% at 6 months	TLF: 4.4% at 6 months	4% at 30 days	-	5.3% at 1 year

ACS acute coronary syndrome, *BVS* bioresorbable vascular scaffold, *Def* definite, *IVUS* intravascular ultrasound, *MACE* major adverse cardiac events, PCI percutaneous coronary intervention, *Prob* probable, *ST* scaffold thrombosis, *TLF* target lesion failure, *TLR* target lesion revascularization, *TVR* target vessel revascularization

be the increased thickness of the BVS struts, which can cause convective flow patterns, potentially triggering platelet deposition and subsequent thrombosis, especially in settings with suboptimal flow conditions. [20] For this reason, BVS with thinner struts are currently being developed and animal studies are ongoing.

Rate of definite ST in the AMC registry was 3.0% at six months. [14] However, in the latter trial, STEMI patients were also included. The annual rate of definite/ probable ST in the GHOST-EU trial was 3.4% and 70% of the ST cases occurred in the first 30 days. In our study, there were three cases of definite ST (1.3%) within one year (table 5 and electronic supplements). In most of these cases, suboptimal implantation in complex lesions was the main finding, with also inadequate DAPT duration in one case. Notably and in contrast to the other registries, no cases of acute or subacute ST occurred. The lower rate of ST in the BVS Expand could presumably be due to the good procedural performance: usage of invasive imaging in almost 40% and pre-dilatation in 89%. Unlike the above-mentioned registries, STEMI patients were excluded in our study. The enrolled patients were all appropriately preloaded with P2Y12 inhibitors which could attribute to the absence of acute and subacute ST, whereas this is not always the case in STEMI patients.

In this study, the presence of with NSTEMI/ UA was not associated with an additional risk of MACE or ST. Theoretically, the lesions in patients with ACS are generally lipid-rich with or without thrombus which will not hinder the deployment nor the expansion of the BVS.

Our analysis shows that underexpansion of BVS occurs frequently and had a non-significant association with an increased risk of MACE and probable/definite ST. Compared to other BVS registries rate of post-dilatation in our study is somewhat low (53.3%) and this could partly explain the frequent occurrence of underexpansion. This low post-dilatation rate was an extension of the ABSORB-EXTEND and ABSORB II studies, where post-dilatation was discouraged as a reflex to a single case where strut fractures were observed due to severe undersizing and post-dilatation with an oversized balloon beyond the expansion limits of the scaffold. This is a different situation compared to underexpansion due to atherosclerotic disease where struts are still apposed but the initial lesions are difficult to dilate. It is now clear that for underexpansion high pressure post-dilatation do not result in strut fractures as long as non-compliant post-dilatation balloons are used within the maximum expansion limit of the implanted device.

Nevertheless, the arbitrary definition of underexpansion we used for this manuscript was partly based on QCA measurements, which are known to underestimate vessel dimensions when compared to invasive imaging methods like IVUS and OCT which is considered the standard at the moment [21, 22]. The difference for IVUS might be even larger compared to OCT, with an underestimation of approximately of QCA of 0.2 mm vs OCT and 0.3 mm vs IVUS. Use of intravascular imaging might improve pre-procedural

vessel sizing, whereas a more liberal use of post-dilatation has to be underlined, with the aim of minimizing BVS underexpansion and, eventually, improving the clinical outcome.

LIMITATIONS

This is a single-center, single-arm registry with no direct comparison with metallic DES. The total number of patients in this study was limited. Thus, these findings warrant further confirmation in a large-scale trial. Ongoing and upcoming trials such as the ABSORB III, IV and the Compare Absorb will provide data derived from larger patient cohorts and in direct comparison to metallic DES.

Furthermore, deciding which patient or lesion was suitable for BVS implantation could have led to selection bias. Almost 80% of the patients returned their study informed consent and thus follow-up is only investigated in these patients. The event rate is unknown in the remaining patients.

CONCLUSION

In our study, BVS implantation in a more complex patient and lesion subset was associated with an acceptable rate of adverse events at the longer term, comparable to rates reported with contemporary second generation metallic drug-eluting stents, while no cases of early thrombosis were observed. This study supports a more extensive use of BVS and launch of randomized trials aiming to demonstrate superiority in the longer term, when optimal implantation strategies are used.

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SUPPLEMENT – NARRATIVES OF CASES WITH ST

Case 1. Neointima hyperplasia and recurrent failure

A 59 year old male patient with a history of CVA and stable angina visited the outpatient clinic. His ECG revealed new T-top inversions. Subsequently, angiography was performed which revealed one vessel disease with narrowing of the proximal LAD (AHA/ACC classification type C lesion) at the origin of the first diagonal (Medina 1,1,0) and a diffusely diseased 2nd ramus marginalis. One BVS (3.5x28mm) was placed with a good results for the main branch without impact on the side branch. 112 days after in the index PCI the patient developed a NSTEMI due to a definite ST. Angiography with additional OCT showed mild scaffold underexpansion (3mm in diameter) with severe neointima development but also areas with late malapposition due to potential vasodilatation and thrombus resorption. Treatment consisted of thrombectomy, eptifibatide and a 3.5x32mm DES (Promus). He was using DAPT (clopidogrel and aspirin) at the time of the event. The patient returned almost 4 months later with unstable angina. There was a severe ISR on angiography (DES failure) with total occlusion and collaterals suggesting resistance to everolimus. It was decided to perform a semi-urgent CABG, which took place four days later.

Case 2. Residual thrombus after BVS implantation

This 69 year old male patient with risk factors of dyslipidaemia and hypertension presented with a NSTEMI. Angiography showed one-vessel disease with narrowing of the proximal and mid LAD (AHA/ACC classification type C lesion). Three BVS (3.0x28mm, 3.5x18mm, 3.5x18mm) were implanted. After implantation, there was pinching and thrombus in the 1st diagonal for which fenestration with a 2.0 mm balloon followed by proximal optimization was performed. Invasive imaging post-procedure revealed organized thrombus behind the struts of the proximal scaffold and thrombus protrusion at the overlapping scaffolds. After 47 days the patient presented with a non-Q wave MI due to a definite ST in the proximal LAD. OCT at the time of the event revealed areas of late malapposition and massive thrombosis. He was treated with thrombectomy, eptifibatide and PCI with a 3.5x38mm DES (Xience) with good angiographic result. The patient was using DAPT (clopidogrel and aspirin). The diagnostic angiography made 110 days later displayed good scaffold and stent apposition on OCT with good coverage of the struts of the new DES.

Case 3. Cardiac death and possible ST

A 76 year old male patient with cardiac risk factors of smoking, diabetes and hypertension, developed angina and dyspnea 66 days after the baseline procedure (one

3.0x18mm BVS in LAD) and suddenly died the next day. No autopsy was performed. The patient was using DAPT (clopidogrel and aspirin).

Case 4. Edge restenosis presenting as acute coronary syndrome

A 65 year old male patient with risk factors smoking, hypertension and a positive family history for CAD, presented with a NSTEMI. Angiography at baseline showed a trifurcation lesion of the LAD and two diagonals treated with pre-dilatation, a single 3.0 x 18 mm BVS and post-dilatation of the main branch only. 142 days later he returned with a NSTEMI. OCT imaging revealed edge restenosis as the underlying mechanism for BVS failure. The patient was treated with 3.5x38 mm DES (Promus) implantation. The patient was using DAPT (aspirin and prasugrel) at time of the event.

Case 5. Discontinuation of anticoagulants

A 70 year old male patient (with extensive vascular disease (diabetes mellitus, dyslipidemia, and hypertension) and decreased LVF.) underwent an elective PCI because of his decreased LV function. Angiography showed a long and calcified lesion in the mid-LAD. Aggressive preparation with a 1.5mm rotablator and dilatations with NC- and cutting balloons were performed and two overlapping BVS (3.0x28mm and 2.5x18mm) were implanted. Five months after the baseline procedure he underwent iliac PTA. Post-PTA the patient developed pain in his back. There was a rise in cardiac enzymes. Because of his surgery, his anticoagulants were briefly interrupted. The patient then developed a NSTEMI due to thrombus in the previously treated LAD with intravascular imaging evidence of underexpansion. Treatment consisted of balloon dilatation and eptifibatide; the thrombus catheter could not approach the lesion. Four days later, the patient developed acute dyspnoea. He had alternating rhythms on ECG (first sinus tachycardia and later a total AV-block). He went to the CCU and was treated with CPAP and a temporary pacemaker. However, he became hemodynamically unstable and CPR was performed because of cardiogenic shock (VF). Sadly, the patient did not survive.

Chapter 6

Are BVS suitable for ACS patients? Support from a large single center real live registry

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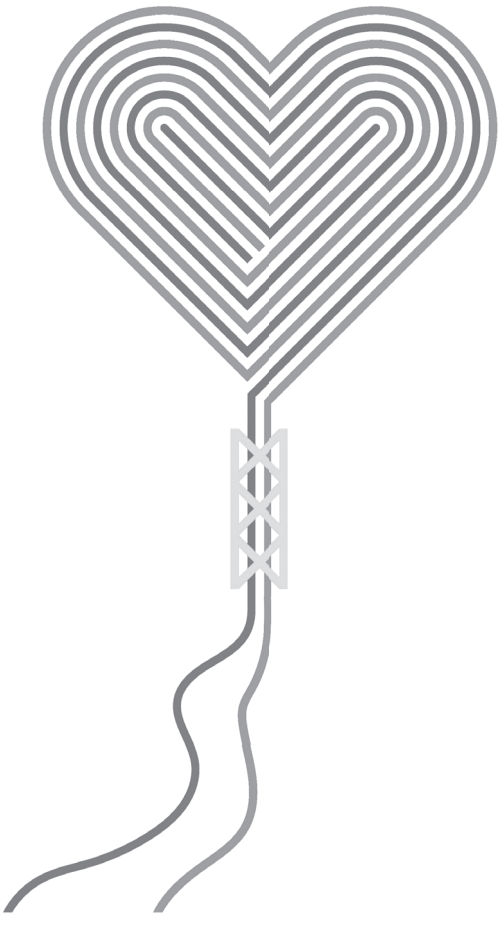

ABSTRACT

Objectives

To investigate one-year outcomes after implantation of a bioresorbable vascular scaffold (BVS) in patients presenting with acute coronary syndrome (ACS) compared to stable angina patients.

Background

Robust data on the outcome of BVS in the setting of ACS is still scarce.

Methods

Two investigator initiated, single-center, single-arm BVS registries have been pooled for the purpose of this study, namely the BVS Expand and BVS STEMI registries.

Results

From September 2012 - October 2014, 351 patients with a total of 428 lesions were enrolled. 255 (72.6%) were ACS patients and 99 (27.4%) presented with stable angina/ silent ischemia. Mean number of scaffold/ patient was 1.55±0.91 in ACS group versus 1.91±1.11 in non-ACS group (P=0.11). Pre- and post-dilatation were performed less frequent in ACS patients, 75.7% and 41.3% versus 89.0% and 62.0% respectively (P=0.05 and P = 0.001). Interestingly, post-procedural acute lumen gain and percentage diameter stenosis were superior in ACS patients, 1.62±0.65mm (versus 1.22±0.49mm, P <0.001) and 15.51±8.47% (versus 18.46±9.54%, P=0.04). Major adverse cardiac events (MACE) rate at 12 months was 5.5% in the ACS group (versus 5.3% in stable group, P=0.90). One-year definite scaffold thrombosis rate was comparable: 2.0% for ACS population versus 2.1% for stable population (P=0.94), however, early scaffold thromboses occurred only in ACS patients.

Conclusions

One-year clinical outcomes in ACS patients treated with BVS were similar to non-ACS patients. Acute angiographic outcomes were better in ACS than in non-ACS, yet the early thrombotic events require attention and further research.

INTRODUCTION

Drug-eluting stents (DES) are the first choice devices in percutaneous coronary interventions (PCI). Despite recent advantages, shortcomings related to the use of DES still are present such as delayed arterial healing, late stent thrombosis (ST), neo-atherosclerosis and hypersensitivity reactions to the polymer. [1, 2]

To overcome these limitations, coronary devices made of fully bioresorbable material were developed to provide mechanical support and drug-delivery within the first year, followed by complete resorption. The first bioresorbable vascular scaffold (BVS) was commercially introduced in September 2012 as the Absorb BVS (Abbott Vascular, Santa Clara, CA). The BVS provides transient vessel support and gradually elutes the antiproliferative drug everolimus. After degradation of the polymer (after approximately two to three years) no foreign material remains and need for late reintervention triggered by foreign material should thus be reduced. [3]

First-in-man trials have proven the safety of the BVS up to five years [4, 5] with a fully completed bioresorption process, a late luminal enlargement due to plaque reduction and a persistent restoration of vasomotion. [6-8] The 1-year results of the larger ABSORB II, ABSORB Japan, ABSORB China and ABSORB III randomized controlled trials comparing BVS with DES (Xience V), confirmed the safety in relatively simple coronary lesions with similar clinical event rates for both devices. [9-12]

In all these early studies, ACS patients were largely excluded while BVS would comprise a more attractive choice in this setting as ACS patients are in general younger with a longer life expectancy, less previous MI and revascularizations with implantation of metallic stents, that would conflict with a therapy aiming at maximal recovery and restoration of normal anatomy of both the coronary artery and myocardium. Furthermore, lesions primarily consisting of soft plaque would be conceptually easy to expand thus facilitating BVS implantation in ACS population. On the other hand, ACS patients are in a much higher pro-thrombotic state which might accelerate thrombus formation on the larger struts of the BVS impacting much more on shear stress compared to the thinner struts of current metallic DES.

Few registries focused on the performance of the BVS in patients presenting with ACS, mainly ST-elevation myocardial infarction (STEMI). BVS STEMI First examined the procedural and short-term clinical outcomes of 49 STEMI patients, revealing excellent results: procedural success was 97.9% and only 1 patient suffered an event (non-target vessel MI). [13] Kočka et al reported similar results in the Prague-19 study. [14] Extending the initial Prague-19 study, the BVS Examination is currently the largest registry on BVS in STEMI with encouraging MACE rates (Device oriented clinical endpoint: 4.1% at one year for both the BVS and the DES), although with a not negligible definite/ probable scaffold thrombosis rate (2.4% at one year for the BVS). [15]

The recently published TROFI II randomized trial investigated arterial healing in 90 STEMI patients treated with a BVS compared to those treated with an everolimus-eluting stent (EES). Based on OCT, arterial healing at 6 months after BVS implantation was non-inferior to that after EES implantation. [16]

In general, the previous studies on BVS in ACS are limited in size and procedural details and there is a need for more data on the efficacy of BVS in the setting of PCI for ACS. The aim of this study was to compare the angiographic and clinical outcomes of BVS in ACS patients with stable patients.

MATERIAL AND METHODS

Population

Two investigator-initiated, prospective, single-center, single-arm studies performed in an experienced, tertiary PCI center have been pooled for the purpose of this investigation. Patients presenting with NSTEMI, stable or unstable angina (UA), or silent ischemia caused by a *de novo* stenotic lesion in a native previously untreated coronary artery with intention to treat with a BVS were included in BVS Expand registry. Angiographic inclusion criteria were lesions with a Dmax (proximal and distal maximal lumen diameter) within the upper limit of 3.8 mm and the lower limit of 2.0 mm by online quantitative coronary angiography (QCA). Complex lesions such as bifurcation, calcified (as assessed by angiography), long and thrombotic lesions were not excluded. Exclusion criteria were patients with a history of coronary bypass grafting (CABG), presentation with cardiogenic shock, bifurcation lesions requiring kissing balloon post-dilatation, ST-elevation myocardial infarction (STEMI) patients, allergy or contra-indications to antiplatelet therapy, fertile female patients not taking adequate contraceptives or currently breastfeeding and patients with expected survival of less than one year. As per hospital policy patients with a previously implanted metal DES in the intended target vessel were also excluded. Also, although old age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age.

Patients presenting with STEMI, were approached to participate in the BVS STEMI Registry, which started two months after the BVS Expand registry. The study design has been described elsewhere. [13] The most important inclusion criteria were presentation with STEMI and complaints < 12 hours. The remaining inclusion criteria were similar to the BVS-EXPAND registry.

Ethics

This is an observational study, performed based on international regulations, including the declaration of Helsinki. Approval of the ethical board of the Erasmus MC was

obtained. All patients undergoing clinical follow-up provided written informed consent to be contacted regularly during the follow-up period of the study.

Procedure

PCI was performed according to current clinical practice standards. The radial or femoral approach using 6 or 7 French catheters were the principal route of vascular access. Pre-dilatation was recommended with a balloon shorter than the planned study device length. Advanced lesion preparation was left to the operator's discretion. Post-dilatation was recommended with a non-compliant balloon without overexpanding the scaffold beyond its limits of expansion (by > 0.5mm larger than nominal diameter). Intravascular imaging with the use of Intravascular Ultrasound (IVUS) or Optical Coherence Tomography (OCT) was used for pre-procedural sizing and optimization of scaffold deployment on the discretion of the operator. All patients were treated with unfractionated heparin (at a dose of 70-100 UI/ kg). Patients with stable angina were preloaded with 300 mg of aspirin and 600 mg of clopidogrel. Patients presenting with ACS were preloaded with 300 mg of aspirin and 60 mg of prasugrel or 180 mg of ticagrelor.

Angiographic analysis

The angiographic analysis was performed by three independent investigators (YI, JF and YO). Coronary angiograms were analyzed with the CAAS 5.10 QCA software (Pie Medical BV, Maastricht, the Netherlands). The QCA measurements provided reference vessel diameter (RVD), percentage diameter stenosis, minimal lumen diameter (MLD), and maximal lumen diameter (Dmax). Acute gain was defined as post-procedural MLD minus pre-procedural MLD (in an occluded vessel MLD value was zero by default).

Follow-up

Survival status of all patients was obtained from municipal civil registries. Follow-up information specific for hospitalization and cardiovascular events was obtained through questionnaires. If needed, medical records or discharge letters from other hospitals were collected. Events were adjudicated by an independent clinical events committee (CEC).

Definitions

The primary endpoint was MACE, defined as the composite endpoint of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). Deaths were considered cardiac unless a non-cardiac cause was definitely identified. TLR was described as any repeated revascularization of the target lesion. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Non-target vessel revascularization was described as any revascularization in a vessel other than the vessel(s) of the target lesion(s). Target lesion failure (TLF)

was defined as a composite endpoint of cardiac death, target vessel MI and TLR. Scaffold thrombosis (ST) and MI were classified according to the Academic Research Consortium (ARC). [17] Clinical device success was defined as successful delivery and deployment of the first study scaffold/ stent at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold/ stent residual stenosis of < 30% as evaluated by QCA. Clinical procedure success was described as device success without major peri-procedural complications or in-hospital MACE (maximum of 7 days).

The intention-to-treat (ITT) group includes all the patients regardless of whether or not the scaffold was successfully implanted. The per-treatment (PT) group consists of all patients in whom the BVS was successfully implanted. All analyses were performed in the PT group.

As a measure of scaffold expansion, the expansion index was calculated as post-procedural MLD divided by nominal device diameter. A cut-off value of < 0.70 below was used to define underexpansion.

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. The student's t test and the chi square test (or Fishers' exact test) were used for comparison of means and percentages. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Kaplan-Meier estimates were compared by means of the log-rank test. For the endpoint MACE, a landmark survival analysis was performed with the landmark time point of 30 days. All statistical tests were two-sided and the P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 21 (IL, US).

A univariate logistic regression analysis was performed to look for predictors of TLF and probable/ definite ST.

RESULTS

From September 2012 up to October 2014, 452 patients were intended to be treated with one or more BVS. Thirteen patients were excluded based on protocol related exclusion criteria of the BVS Expand registry and the BVS STEMI registry and 79 patients declined to participate in one of the two follow-up registries. Thus 360 patients (intention-to-treat group) remained for the purpose of this study. There were 9 cases of device failure in which a metallic stent was implanted and the per-treatment group consisted of 351 patients. A flowchart of the study is given in figure 1.

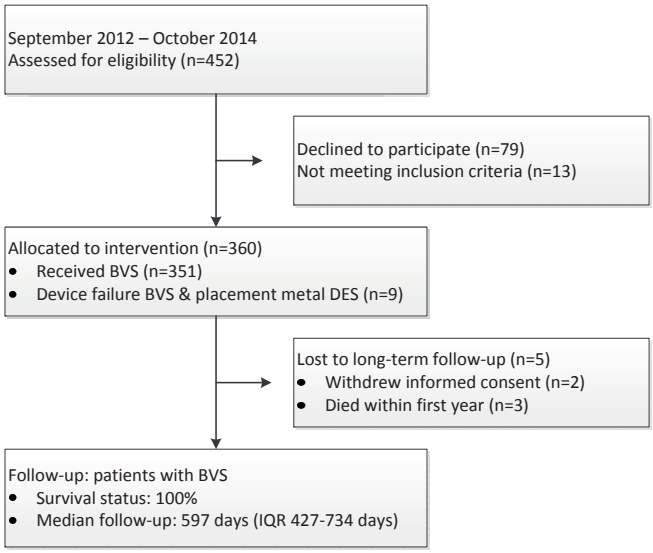

Figure 1 Flowchart

Baseline characteristics

Baseline characteristics are presented in table 1. Presentation with ACS was present in 72.6% of the patients and 27.4% were stable patients. Mean age was significantly different between the two groups: 57.9 ± 10.7 years for ACS patients and 63.4 ± 8.9 years for non-ACS patients (P < 0.001). Dyslipidemia, history of MI, history of PCI and renal insufficiency were factors that occurred significantly more frequent in stable patients. ACS patients had more single vessel disease (71.5% versus 54.2%, P = 0.02).

Lesion characteristics are presented in table 2. In both groups, the left anterior descending coronary artery (LAD) was most commonly treated (48.0% in ACS group and 54.4% in non-ACS group, P = 0.23). Lesions in stable patients were more complex, with a higher percentage of AHA/ ACC type B2/ C lesions. Pre-procedural TIMI flow was significantly different (P <0.001). The mean lesion length was comparable in both groups (24.58 ± 14.58 mm for non-ACS versus 22.41 ± 12.24 mm for ACS, P = 0.35) (table 3). Pre-procedural QCA analysis revealed significant differences between the groups in MLD: 0.69 ± 0.51 mm for ACS patients versus 1.04 ± 0.40 in stable patients (P <0.001). After excluding the thrombotic total occlusions, this statistical difference remained (0.89 ± 0.39 mm for ACS versus 1.06 ± 0.37 mm for non-ACS, P = 0.002). Pre-procedural %DS was 65.45 ± 20.91% in the ACS group versus 58.62 ± 13.84% in non-ACS group (P <0.001). Post-procedural QCA measurements revealed a superior acute performance in the ACS population: remaining %DS was significant lower (15.57 ± 8.47% versus 18.46 ± 9.54%, P = 0.04). Final MLD was larger (2.35 ± 0.42 mm versus 2.26 ± 0.38 mm, P = 0.05) and also acute lumen gain was higher (1.62 ± 0.65 mm versus 1.22 ± 0.49 mm, P <0.001).

Table 1. Patient characteristics

	ACS patients	Non-ACS patients	P value
Number of patients (%)	255 (72.6)	96 (27.4)	
Mean age in years (±SD)	57.9 ± 10.7	63.4 ± 8.9	<0.001
Gender (%)			
Male	191/255 (74.9)	73/96 (76.0)	0.84
Female	64/255 (25.1)	23/96 (24.0)	0.84
Smoking (%)	149/255 (58.4)	44/96 (45.8)	0.03
Hypertension (%)	130/253 (51.0)	55/95 (57.3)	0.29
Dyslipidemia (%)	92/251 (36.1)	49/95 (51.0)	0.01
All diabetes mellitus (%)	33/255 (12.9)	18/98 (18.8)	0.16
Insulin dependent	7/255 (2.7)	3/96 (3.1)	1.00
Family history of CAD (%)	104/252 (40.8)	39/94 (41.5)	0.94
History of MI (%)	25/255 (9.8)	21/96 (21.9)	0.003
History of PCI (%)	12/255 (4.7)	12/96 (12.5)	0.01
Cardiogenic shock (%)	5/255 (2.0)	0/96 (0.0)	0.33
Renal insufficiency (%)	8/255 (3.1)	8/88 (8.3)	0.046
Presentation (%)			<0.001
Stable angina	0/255 (0.0)	95/96 (99.0)	
Unstable angina	40/255 (15.6)	0/96 (0.0)	
STEMI	120/255 (46.9)	0/96 (0.0)	
NSTEMI	95/255 (37.3)	0/96 (0.0)	
Silent ischemia	0/255 (0.0)	1/96 (1.0)	
Single vessel disease (%)	183/255 (71.5)	52/96 (54.2)	0.02
P2Y12 inhibition use			<0.001
Clopidogrel	60/255 (23.5)	86/96 (89.6)	
Prasugrel	164/255 (64.3)	9/96 (9.4)	
Ticagrelor	30/255(11.8)	1/96 (1.0)	

Values are expressed as percentages or mean ± standard deviation when appropriate. P values are based on Chi square test or Fishers' exact test for categorical variables and Student's *t* test for continuous variables. ACS: acute coronary syndrome, CAD: coronary artery disease, MI: myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, PCI: percutaneous coronary intervention, STEMI: ST elevation myocardial infarction

Table 2. Lesion characteristics

	ACS patients N= 255, L=300	Non-ACS patients N= 96, L=128	P value
Number of lesions per patient	1.18 ± 0.49	1.33 ± 0.56	
Left anterior descending artery (%)	48.0	54.4	0.23
Left circumflex artery (%)	24.3	20.0	0.38
Right coronary artery (%)	27.7	25.6	0.61
Bifurcation (%)	20.3	30.7	0.009
Calcification (moderate or severe) (%)	31.8	50.4	<0.001
(Chronic) total occlusion*	26.2	8.7	<0.001
CTO	1.7	7.0	0.007
ACC/ AHA lesion classification (%)			
A	14.1	15.0	0.75
B1	53.4	41.7	0.02
B2	24.2	22.0	0.66
C	7.2	19.7	<0.001
TIMI			
Pre-procedure			<0.001
TIMI 0	25.2	9.4	
TIMI I	4.6	0.8	
TIMI II	16.1	6.3	
TIMI III	52.1	81.9	
Post-procedure			0.61
TIMI 0	0.0	0.0	
TIMI I	0.3	0.0	
TIMI II	4.6	3.1	
TIMI III	93.4	95.3	

Values are expressed as percentages or mean ± standard deviation when appropriate. P values are based on Chi square test or Fishers' exact test for categorical variables and Student's *t* test for continuous variables. ACS: acute coronary syndrome (ST-elevation myocardial infarction, non-ST myocardial infarction and unstable angina), non-ACS: non acute coronary syndrome (stable angina and silent ischemia)

Procedural details

Procedural and angiographic details are summarized in table 3. In ACS patients, predilatation was performed in 75.7% of the lesions, compared to 89.0% in stable patients (P = 0.05). Pre-dilatation balloon to artery ratio was comparable (1.01 ± 0.21 versus 1.05 ± 0.25, P = 0.11). Post-dilatation was significantly less frequently performed in the ACS group (41.3% versus 62.2%, P = 0.001). Advanced lesion preparation was less often performed in ACS patients than in stable patients (rotational atherectomy: 1.0% versus 5.6%, P = 0.02; scoring balloon 1.3% versus 3.9%, P = 0.14). A total of 582 BVS were

Table 3. Procedural and angiographical characteristics

	ACS N= 255, L=300	Non-ACS N= 96, L=128	P value
Procedural characteristics			
Aspiration (%)	34.4	0.0	<0.001
Rotablation (%)	1.0	5.6	0.02
Scoring balloon (%)	1.3	3.9	0.14
Invasive imaging at baseline (%)			
OCT	25.2	36.2	0.10
IVUS	9.9	24.8	<0.001
Pre-dilatation (%)	75.7	89.0	0.05
Pre-dilatation balloon : artery ratio	1.01 ± 0.21	1.05 ± 0.25	0.11
Maximum pre-dilatation balloon diameter (mm)	2.57 ± 0.42	2.60 ± 0.34	0.49
Maximum pre-dilatation inflation pressure (atm)	13.96 ± 3.02	14.01 ± 3.41	0.91
Buddy wire	9.8	10.2	0.74
Daughter catheter	3.6	4.0	0.80
Total number of scaffolds implanted	394	183	
Mean number of scaffolds/ patient	1.55 ± 0.91	1.91± 1.11	0.11
Mean number of lesions/ patient	1.18 ± 0.49	1.33 ± 0.56	0.015
Mean scaffold diameter (mm)	3.14 ± 0.37	3.02 ± 0.38	0.003
Mean scaffold length (mm)	20.35 ± 5.67	20.75 ± 5.99	
Overlap (%)	20.7	31.5	0.04
Post-dilatation (%)	41.3	62.2	0.001
Post-dilation balloon: mean scaffold diameter ratio	1.23 ± 0.21	1.31 ± 0.23	0.11
Maximum post-dilatation balloon diameter (mm)	3.38 ± 0.42	3.19 ± 0.42	0.003
Maximum post-dilatation inflation pressure (atm)	15.40 ± 3.00	16.10 ± 3.31	0.17
Clinical device success (%)	98.0	97.7	0.82
Clinical procedural success (%)	95.4	96.9	0.49
Angiographical characteristics			
Mean lesion length (mm)	22.41 ± 12.24	24.58 ± 14.58	0.35
Pre-procedure, overall			
RVD (mm ± SD)	2.65 ± 0.54	2.57 ± 0.45	0.22
MLD (mm ± SD)	0.69 ± 0.51	1.04 ± 0.40	<0.001
DS (%)	64.82 ± 42.0	47.94 ± 43.48	<0.001
Pre-procedure, non-total occlusion			
RVD (mm ± SD)	2.60 ± 0.48	2.58 ± 0.44	0.72
MLD (mm ± SD)	0.89 ± 0.39	1.06 ± 0.37	0.002
In-scaffold DS (%)	65.45 ± 20.91	58.62 ± 13.84	0.002
Pre-procedure, total occlusion (L=80 for ACS and L=11 for non-ACS)			
RVD (mm ± SD)	2.81 ± 0.69	1.78 ± 1.34	<0.001

Table 3. Procedural and angiographical characteristics (*continued*)

	ACS N= 255, L=300	Non-ACS N= 96, L=128	P value
Post-procedure, overall			
RVD (mm ± SD)	2.79 ± 0.48	2.77 ± 0.43	0.66
MLD (mm ± SD)	2.35 ± 0.42	2.26 ± 0.38	0.05
In-scaffold DS (%)	15.57 ± 8.47	18.46 ± 9.54	0.04
Acute gain (mm ± SD)	1.62 ± 0.65	1.22 ± 0.49	<0.001

Values are expressed as percentages or mean ± standard deviation when appropriate. *P* values are based on Chi square test or Fishers' exact test for categorical variables and Student's *t* test for continuous variables. *ACS*: acute coronary syndrome (ST-elevation myocardial infarction, non-ST myocardial infarction and unstable angina), *non-ACS*: non acute coronary syndrome (stable angina and silent ischemia), *%DS*: percentage diameter stenosis, *IVUS*: intravascular imaging, *OCT*: optical coherence tomography, *MLD*: minimal lumen diameter, *RVD*: reference vessel diameter

implanted: 399 in the ACS group (with a mean of 1.55 ± 0.91 scaffolds per patient) and 183 in stable patients (with a mean of 1.91 ± 1.11 per patient in stable patients).

In the ACS population 6 cases of device failure occurred, all due to delivery failure. Main causes of these delivery failures were calcification and angulation (see table 6 for details). Eight in-hospital MACE were reported. Whereas in the stable population 3 device failures (placement metal DES due to dissection after BVS implantation and delivery failures due to severe calcification and tortuosity) and no in-hospital MACE were documented.. Clinical device and procedural success were 98.0% and 95.4% for the ACS population and 97.7 and 96.9% respectively for stable patients.

Clinical outcomes

Data on survival status was available in 100% with a median follow-up period of 731 days (interquartile range [IQR]: 550-769 days). A total of 340 (96.9%) patients had a follow-up duration of at least 365 (± 2) days.

Cumulative clinical events rates are summarized in table 4. Clinical outcomes appeared to be comparable with no significant difference between patients presenting with ACS as compared to stable patients. Rate of death was 0.0% in the ACS group versus 3.1% in the non-ACS group (P = 0.06). Three patients died within the first year. One patient, with extensive cardiovascular disease died at day 166, 4 days after he went through a definite ST and MI, most probably due to a brief interruption of his antithrombotic medication during an elective surgery. The second patient died a few days after his prostate was surgically removed. In this case, dual antiplatelet inhibition therapy (DAPT) was also shortly interrupted causing a MI (probable ST). The last patient died of a sudden cardiac death 66 days after baseline PCI (possible ST)

MACE rate in the ACS population was comparable to the non-ACS population (5.5% versus 5.3%, P = 0.90, figure 2). MACE was mainly driven by MI and TLR. TLR rate was comparable in both groups. Rate of TVR was in 3.2% in ACS patients versus 3.5% in stable patients (P = 0.86). Non-TVR rate was 3.2% and 5.5% in respectively ACS and non-ACS patients (P = 0.35). Rate of definite ST was similar in both groups: 2.0% in the ACS group versus 2.1% in stable patients (P = 0.94). Of note, early ST only occurred in the ACS group, late thrombosis was more prevalent in stable patients (table 4 and figure 3B).

Table 4. Clinical outcomes at one year

	ACS (N=255)	Non-ACS (N=96)	P value
All-cause death (%)	0.0 (0)	3.2 (3)	0.05
Cardiac	0.0 (0)	3.2 (3)	0.05
Non-Cardiac	0.0 (0)	0.0 (3)	-
MACE (%)	5.5 (14)	5.3 (5)	0.90
Myocardial infarction (%)	5.1 (13)	2.1 (2)	0.22
Target lesion revascularization (%)	3.1 (8)	3.2 (3)	0.99
Target vessel revascularization (%)	3.5 (9)	3.2 (3)	0.86
Non-target vessel revascularization (%)	3.2 (8)	5.5 (5)	0.35
Overall scaffold thrombosis* (%)	2.4 (6)	4.2 (4)	0.37
Definite scaffold thrombosis (%)	2.0 (5)	2.1 (2)	0.94
Acute	1.2 (3)	0.0 (0)	0.29
Subacute	0.4 (1)	0.0 (0)	0.54
Late	0.4 (1)	2.1 (2)	0.12
Definite/ probable scaffold thrombosis (%)	2.4 (6)	2.1 (2)	0.88
Acute	1.2 (3)	0.0 (0)	0.29
Subacute	0.4 (1)	0.0 (0)	0.54
Late	0.8 (2)	2.1 (2)	0.30

Event rates are summarized as %. P values are based on log rank test for comparing Kaplan Meier. MACE: major adverse cardiac events (composite endpoint consisting of cardiac death, myocardial infarction and target lesion revascularization). *Includes definite, probable and possible ST.

A landmark survival analysis of MACE, definite/ probable ST, MI and TLR indicated a trend for higher event rates of the ACS population in the short-term (< 30 days). Conversely, mid-term event rates were higher in stable patients, although log rank test failed to prove significance (figure 3A-3D).

In a univariate analysis of TLF the following characteristics tended to be related by at least a twofold increase in odds ratio (OR): renal insufficiency, bifurcation, male gender and age above 65 years (table 5). The use of intravascular imaging at baseline might be protective for TLF (OR 0.49, P = 0.22).

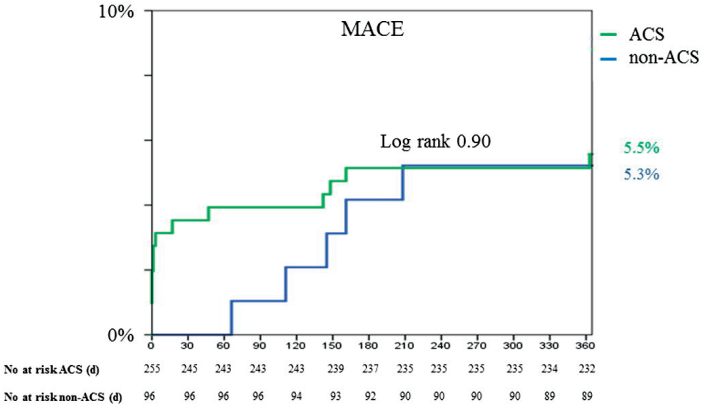

Figure 2 Kaplan-Meier curve for MACE

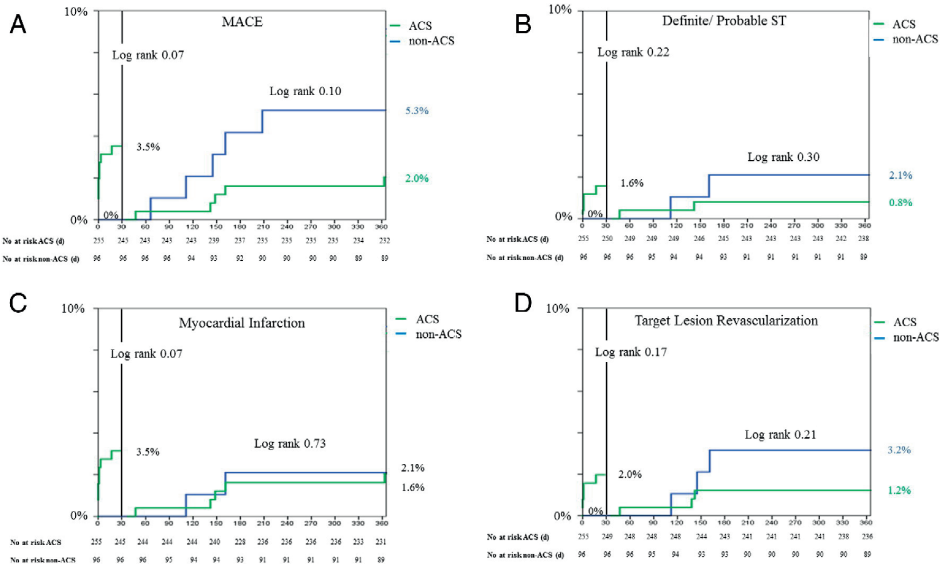

Figure 3 A - D Landmark survival analysis for MACE, probable/definite ST, MI and TLR.

Table 5. Univariate analysis of TLF

	Odds ratio ACS vs. non ACS (95% confidence interval)	P value
Renal insufficiency	3.28 (0.68 – 15.83)	0.14
Bifurcation	2.68 (0.98 – 7.36)	0.06
Male gender	2.38 (0.53 – 10.69)	0.26
Age above 65 years	2.10 (0.77 – 5.75)	0.15
History of MI	1.57 (0.43 – 5.73)	0.50
Small vessel (< 2.5mm)	1.54 (0.56 – 4.20)	0.40
Post-procedural TIMI 0/1	1.45 (0.53 – 3.99)	0.47
Underexpansion	1.30 (0.46 – 3.66)	0.62
Calcification	1.26 (0.46 – 3.46)	0.66
Long lesion (>32 mm)	1.20 (0.33 – 4.36)	0.78
Smoking	1.07 (0.74 – 1.54)	0.72
Diabetes Mellitus	0.83 (0.18 – 3.78)	0.81
Presentation with ACS	0.82 (0.28 – 2.43)	0.72
Intravascular imaging at baseline	0.49 (0.15 – 1.54)	0.22

ACS: acute coronary syndrome, *MI*: myocardial infarction, *TLF*: target lesion failure (cardiac death, target vessel *MI*, ischemia driven *TLR*)

DISCUSSION

The present study reports on the comparative procedural and the one-year clinical outcomes of ACS patients versus non-ACS patients treated with an Absorb bioresorbable scaffold. The main findings of this study are summarized as follows: 1) Angiographic outcomes were better in ACS patients despite the fact that less aggressive lesion preparation and less frequent post-dilatation were performed; 2) Overall one-year ST rate in ACS patients was similar to the non-ACS patients. Interestingly, early definite ST occurred only in the ACS population while late ST seemed more frequent in stable patients.; 3) Despite the higher rate of early complications in the ACS group, landmark analyses after one month demonstrated that event rates were lower in this group than the stable patient group; 4) Clinical outcomes at one year were comparable among ACS and stable patients.

Differences between ACS patients and stable patients exist at multiple levels. On a patient level, patients presenting with ACS often are younger and thus have a longer life expectancy. Cardiovascular disease in this group is less extensive when compared to stable patients. Additionally, a different plaque composition is present, featured by a lipid-rich necrotic core with a thin fibrous cap. All these factors make ACS patients very attractive for bioresorbable technologies where full expansion is important and acute recoil a concern. Moreover, in ACS patients DAPT pretreatment is usually short

Table 6. Details device failures in ACS population

	Age (yr)	Gender	Presentation	Culprit	Location	AHA/ ACC	Calc.	Bif.	Ang.	Tort.	Additional device	Treatment
1	71	m	NSTEMI	RCA	RCA	B2	severe	no	no	no	PT Graphix Super Support	3.0x28, 3.0x28 Xience
2	37	m	UAP	RCA	LCx	B1	no	no	yes	no	none	2.5x12 Xience
3	60	m	UAP	LCx	LCx	B2	moderate	no	yes	no	none	2.5x18, 2.25x12 Xience
4	47	m	STEMI	LAD	LAD	B2	no	yes	no	yes	STO1 Heartrail	3.5x23 Xience
5	71	f	UAP	RCA	RCA	B2	severe	no	no	no	rotablator	4 Promus stents
6	59	m	UAP	LCx	LCx	B2	severe	yes	yes	no	STO1 Heartrail	3.5x8 Xience

Ang = Angulation, Bif = Bifurcation, Calc = Calcification, NSTEMI: non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction, Tort: Tortuosities, UAP: unstable angina pectoris

(especially in STEMI patients) and frequently not yet resulting in active platelet function inhibition, while the thrombus burden is greater with high platelet activation and a systemic inflammatory response. These factors might amplify the risk of acute thromboses and cause a higher risk of MACE. For these reasons studies like ours are important to investigate the suitability of BVS in ACS patients. To the best of our knowledge, no data is available comparing the performance of BVS in ACS with stable patients compared to stable patients.

The BVS Expand registry and the BVS STEMI registry are two single-center, single-arm registries describing procedural clinical outcomes of patients treated with BVS. At variance of previous studies investigating the Absorb bioresorbable scaffold, all events were adjudicated by an independent clinical event committee (CEC). Also, all angiograms were analyzed using QCA. Lastly, combining the results of the two registries, both handling less restrictive inclusion criteria, we were able to create a study population reflecting a real-world population with a considerable amount of ACS patients.

The superior acute angiographic outcome in ACS patients compared to stable patients is an important observation. In previous studies it was demonstrated that the acute performance of the Absorb scaffold is somewhat inferior to metallic stents for stable angina patients. For example, in-device acute lumen gain in the ABSORB II trial was 1.15 ± 0.38 mm in BVS group versus 1.46 ± 0.38 mm in the EES group ($P < 0.001$). In the ABSORB III trial reported lumen gain was 1.45 ± 0.45 mm versus 1.59 ± 0.44 mm ($P < 0.001$). Finally, in the ABSORB Japan and ABSORB China trials acute lumen gain numbers were as follows: 1.46 ± 0.40 mm versus 1.65 ± 0.40mm ($P < 0.0001$) and 1.51 ± 0.03 versus 1.59 ± 0.03 ($P = 0.04$) respectively. Remarkably, in STEMI patients no difference in acute gain was observed between BVS and DES (2.16 ± 0.52 mm versus 2.21 ± 0.56 mm, $P = 0.57$). This finding also suggests that the somewhat inferior angiographic results only imply for stable angina patients while the current semi-compliant balloon and wide strut BVS design are sufficient for the general softer plaque composition of ACS patients. In the current study, post-dilatation was significantly less frequently performed in ACS patients, however angiographic outcomes were better. Post-procedural MLD, RVD, %DS and in-scaffold acute lumen gain were all superior compared to post-procedural QCA measurements in stable patients. These promising angiographic results in ACS patients support the use BVS in this setting as they are predictive for clinical events.

Overall, one-year ST rate in ACS patients was similar to the non-ACS patients. The observed rate of early ST in the ACS population might raise some concerns. Previous studies have stated that presentation with ACS is an independent risk factor for the development of (metal) stent thrombosis. [18-20] Using metal devices, multiple studies have documented that stenting of lesions with appeared plaque rupture are prone to delayed healing, characterized by higher percentages of uncovered, malapposed and protruding stent struts with a subsequent risk of stent thrombosis. [21-24] Furthermore,

underexpansion appeared to be an important predictor. [25-27] This is also the case for ST in BVS patients. [28, 29] In ACS patients, high thrombus burden, increased platelet activation and vasospasm are mechanisms that trouble optimal sizing resulting in higher rates of malapposition. In the acute setting, lesion preparation using pre-dilatation and intravascular imaging are less frequently performed than in stable patients. Although the acute scaffold expansion is on average better in the ACS population than in the stable population, it is very important to properly size the vessel and to optimize the final scaffold expansion in order to avoid early ST.

The landmark analysis beyond one month up to 12 months showed favorable results with regard to ST and TLR for the ACS patients (0.8% and 1.2% respectively). The somewhat higher event rates in the non-ACS group are a representation of a more complex non-study real world patient population. Therefore, the one-year MACE (composite of cardiac death, MI and TLR) rates of 5.5% (ACS) and 5.3% (non-ACS) are acceptable and comparable to trials using BVS in relatively simple lesions: 5.0% in the ABSORB II trial and 3.8% in the ABSORB China trial. [9, 12]. A comparable endpoint, target lesion failure (TLF: composite endpoint consisting of cardiac death, target vessel MI and ischemia driven TLR), in the ABSORB III and ABSORB Japan trials were 7.8% and 4.2% respectively. [10, 11] In these studies, STEMI patients were excluded. Compared to studies investigating clinical outcomes of metal DES in STEMI patients, event rates in our report are higher than for EES but for lower compared to first-generation DES. [30, 31]

Recently, few concerns were raised concerning a potentially increased incidence of ST after implantation of a BVS. [27, 32-34] Also, in our registry rate of definite ST (2.0% for ACS patients and 2.1% for stable patients) was higher compared to that of currently available metallic DES. [35, 36] The importance of patient selection, lesion preparation, pre- and post-dilatation and also the consideration of intra-vascular imaging have to be underlined. [37, 38] A pilot imaging study suggested suboptimal implantation as an important cause for BVS ST. [28] Use of intravascular imaging could improve pre-procedural vessel sizing, optimize lesion coverage and eventually reduce adverse events

Next generation BVS with smaller scaffold struts may reduce the early event rates in ACS patients. For the current design, using more potent P2Y12 inhibitors such as ticagrelor, a direct-acting platelet inhibitor or cangrelor, an intravenous antiplatelet drug, could be valuable. In the ATLANTIC trial, ticagrelor was administered prehospital in the ambulance to STEMI patients, leading to a reduction in ST rate. [39] The CHAMPION PHOENIX trial assessed ischemic complications of PCI after administration of cangrelor and showed a decrease in these complications, with no significant increase in severe bleeding. [40] The upcoming HORIZONS-ABSORB AMI will compare the performance of BVS to DES when cangelor is used on top of heparin or bivalirudin in STEMI patients. [41]

Rate of mortality in ACS patients is worse compared with patients who present with stable CAD. [42-45] In our patient cohort, mortality was zero percent in the ACS population

probably reflecting our exclusion criteria for the STEMI population (exclusion of patients presenting with cardiogenic shock). As shown by our landmark survival analyses, events in the ACS group are especially clustered in the early phase after BVS implantation. On the other hand, one-year Kaplan Meier curves for events are lower in ACS patients. This is probably due to patient selection, where ACS patients present with different patient and lesion factors (younger age, less extensive cardiovascular disease and more often simple lesions), and the higher intake of prasugrel and ticagrelor in these patients (76.1% versus 10.4%).

In summary, our results warrant further confirmation in a large-scale trial with a high number of ACS patients and an optimal implantation strategy tailored at the limitation of this first generation fully bioresorbable scaffolds. Ongoing and upcoming trials such as the AIDA, Compare Absorb (NCT02486068) and HORIZON-ABSORB AMI, will provide data derived from larger patient cohorts and in direct comparison to metallic DES. [41, 46]

LIMITATIONS

These results are derived from two single-center, single-arm registries with no direct comparison with metallic DES. The total number of patients in this study was limited.

Baseline differences in patient and lesion characteristics could have led to biased outcome in clinical event rates.

Furthermore, deciding which patient or lesion was suitable for BVS implantation could have led to selection bias. However, there was a fair amount of patients presenting with ACS and with B2/C lesions were included, indicating the complexity of the present study population.

CONCLUSION

Despite the higher rate of early complications due to early ST in the ACS population, the one-year clinical outcomes for BVS implantations in ACS patients versus non-ACS patients are comparable. The early ST rate observed in ACS needs further attention and optimized antiplatelet therapy may play a role. Angiographic outcomes for BVS in ACS patients are at least as good as non-ACS patients. Therefore, ACS patients may be suitable candidates for the treatment with the BVS if early procedural related complications can be avoided.

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Chapter 7

Initial experience with everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with acute myocardial infarction

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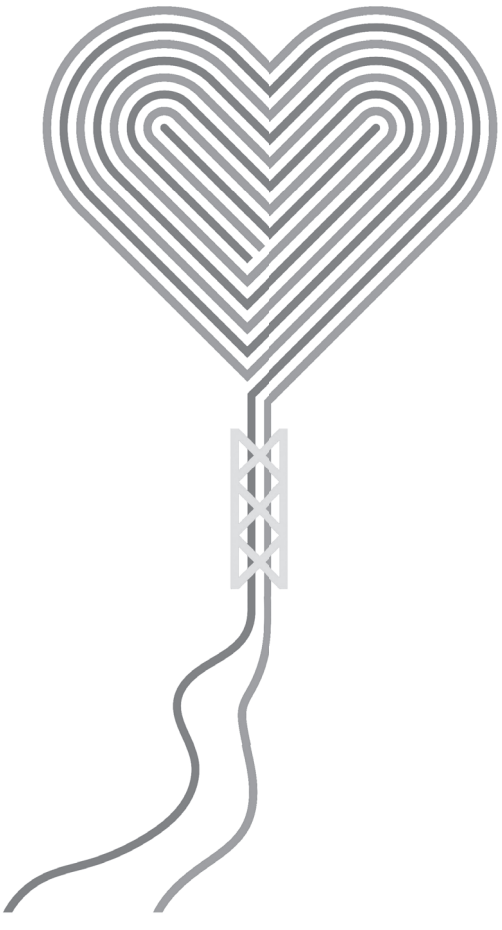

ABSTRACT

Background

Very limited data are currently available on mid-term outcomes after implantation of everolimus eluting bioresorbable scaffolds (BVS) for treatment of acute myocardial infarction.

Methods and Results

Patients presenting with STEMI and undergoing primary percutaneous coronary intervention, with BVS were evaluated and compared with patients treated with everolimus-eluting metal stents (EES) by applying propensity matching. Quantitative coronary angiography analysis and 18-month clinical follow-up were reported.

A total of 302 patients were analysed, 151 with BVS and 151 with EES. Baseline clinical characteristics were similar between groups. Final TIMI 3 flow was 87.4% vs 86.1% p= 0.296. At 18-month follow-up, all-cause mortality was 2.8 vs 3.0 in the BVS and EES group respectively p=0.99, MACE rate was higher in the BVS group 9.8% vs 3.6% p=0.02. Target lesion revascularizations was 5.7% vs 1.3% p=0.05. The 30-day MACE rate in BVS patients without post-dilatation was 6.8% in patients with post-dilatation was 3.6%. Scaffold thrombosis (ST) occurred primarily in the acute phase (acute ST 2.1% vs 0.7%, p=0.29; subacute 0.7% vs 0.7%, p=0.99; late 0.0% vs 0.0%; very late1.5% vs 0.0%, p=0.18). The majority of the cases with acute ST had no post-dilatation at the index procedure (3/4 cases)

Conclusions

Patients implanted with BVS showed an overall higher rate of clinical events compared with metal stents. The majority of clinical events occurred in the early phase after implantation and mainly in cases without post-dilatation. Optimisation of the implantation technique could be relevant also in acute patients.

INTRODUCTION

Bioresorbable vascular scaffolds (BVS) have been recently introduced as a novel approach for treatment of coronary artery disease, providing transient vascular support and drug delivery potentially restoring the vascular physiology after device bioresorption.[1-4]

The theoretical advantages of this novel technology such as late lumen enlargement restoration of coronary vasomotion and plaque sealing could suggest this device as particularly appealing for in patients with thrombotic soft plaques._ENREF_5 [5-7] Bioresorbable vascular scaffolds have been hypothesized to be particularly suitable for acute thrombotic lesion, which are frequently soft necrotic core rich plaques with a ruptured thin fibrotic cap.[8] Vessels with such lesions, could benefit the most from a treatment with bioresorbable devices leading to the so-called restoration therapy, represented by late lumen enlargement and re-acquisition of coronary vasomotion.[9, 10] Due to vasoconstriction and presence of thrombus, the treatment of acute lesions is often associated with device under-sizing and the occurrence of malapposition after thrombus dissolution. Theoretically, the complete bioresorption of the device would avoid the presence of long-term malapposed struts. In addition the BVS wider struts have been hypothesized to play a role in thrombotic material entrapment with a possible impact on distal embolization. In addition, polymer bioresorption and concomitant formation of a neointimal layer given by connective tissue and smooth muscle cells could stabilize the plaque creating a neo-thick fibrous cap, without the long term permanence of metallic material in the vessel wall. [5]

Initial small cohort studies with short follow-up and relatively selected populations reported encouraging results after BVS implantation in acute patients; however, at the current state of the art limited data are available on the mid-term performance of this novel device in patients presenting with acute myocardial infarction.[11-13] Given this background, we analyzed patients presenting with ST-elevation myocardial infarction treated with BVS and we compared angiographic and 18-month clinical results with a matched population implanted with everolimus- eluting stents (EES).

METHODS

Patients presenting with ST-segment elevation myocardial infarction and treated with BVS at the Thoraxcenter, Erasmus MC in Rotterdam between 1 November 2012 and 31 December 2014, were evaluated for the present analysis. Subjects included were patients ≥18-years old admitted with ST-segment elevation myocardial infarction (STEMI). Culprit lesions were located in vessels within the upper limit of 3.8 mm and the lower limit of 2.0 mm by online quantitative coronary angiography (QCA). The BVS

was implanted according to the manufacturer's indication for target-vessel diameter ranges and BVS diameters to be used. The BVS with a nominal diameter of 2.5 mm was implanted in vessels ≥2.0 and ≤3.0 mm by online QCA; the 3.0 mm BVS was implanted in vessels ≥2.5 and ≤3.3 mm by online QCA; the 3.5 mm BVS was implanted in vessels ≥3.0 and ≤3.8 mm. For each nominal diameter a further expansion of 0.5 mm was allowed. All patients were treated with unfractionated heparin at the dose of 70–100 UI/kg and dual antiplatelet therapy after treatment was planned to have a duration of 12 months. Exclusion criteria comprised pregnancy, known intolerance to contrast medium, uncertain neurological outcome after cardiopulmonary resuscitation, previous percutaneous coronary intervention with the implantation of a metal stent, left main (LM) disease, previous coronary artery bypass grafting (CABG), and participation in another investigational drug or device study before reaching the primary endpoints.

Propensity score was applied to match each STEMI patient treated with BVS to a comparable patient treated with everolimus-eluting stent (EES) at the same institution.

Baseline and post-scaffold/stent implantation quantitative coronary angiographic analysis, optical coherence tomography (when available) analyses at post- scaffold/stent implantation were performed. Clinical outcomes at the 18-month follow-up were evaluated. (Figure 1)

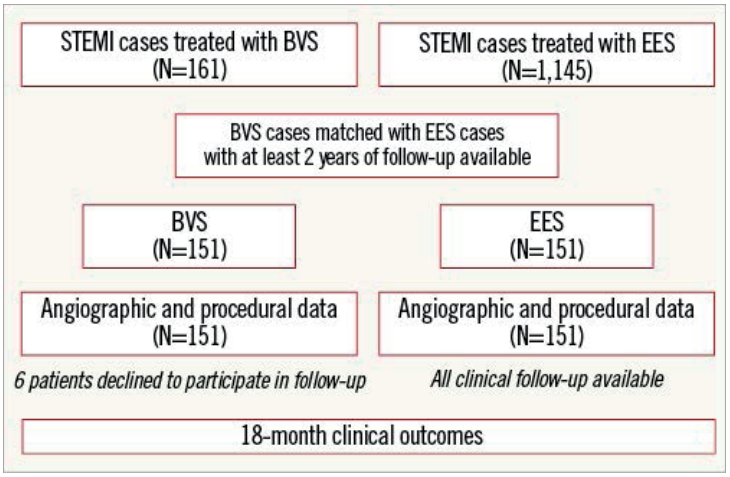

Figure 1 Flow chart of the study.

Study device

The second-generation BVS (Absorb BVS, Abbott Vascular, Santa Clara, CA) is a balloon-expandable scaffold consisting of a polymer backbone of poly-L-lactide (PLLA) coated with a thin layer of a 1:1mixture of an amorphous matrix of poly- D, L-lactide (PDLLA) polymer and 100 μg/cm^2 of the antiproliferative drug everolimus. Two platinum mark-

ers located at each BVS edge allow for accurate visualization of the radiolucent BVS during angiography or other imaging modalities. The PDLLA controls the release of everolimus, 80% of the drug is eluted within the first 30 days. Both PLLA and PDLLA are fully bioresorbable. The polymers are degraded via hydrolysis of the ester bonds, and the resulting lactate and its oligomers are transformed to pyruvate and metabolized in the Krebs cycle. Small particles, less than 2 µm in diameter, have also been shown to be phagocytized and degraded by macrophages. According to preclinical studies, [14] complete bioresorption of the polymer backbone occurs from is 2 to 3 years after implantation.[15]

Control device

The everolimus eluting coronary stent system is a balloon-expandable metallic platform stent manufactured from a flexible cobalt chromium alloy with a multicellular design and coated with a thin non-adhesive, durable, biocompatible acrylic, and fluorinated everolimus-releasing copolymer.

Quantitative coronary angiographic analysis

Angiographic views with minimal foreshortening of the lesion and limited overlap with other vessels were used whenever possible for all phases of the treatment. Comparison between pre and post treatment, were performed in matched angiographic views. In case of thrombotic total occlusion, pre-procedure quantitative coronary angiographic analysis was performed as proximally as possible from the occlusion (in case of a side branch distally to the most proximal take off of the side branch), as already reported.[11] Intracoronary thrombus was angiographically identified and scored in five grades as previously described.[16, 17] Thrombus grade was assessed before procedure and after thombectomy. The two-dimensional angiograms were analysed with the CASS 5.10 analysis system (Pie Medical BV, Maastricht, the Netherlands). In each patient, the treated region and the peri-treated regions (defined as 5 mm proximal and distal to the device edge) were analysed. The QCA measurements included reference vessel diameter (RVD), percentage diameter stenosis, minimal lumen diameter (MLD), and maximal lumen diameter (Dmax). Acute gain was defined as post-procedural MLD minus pre-procedural MLD (MLD value equal to zero was applied when culprit vessel was occluded pre-procedurally).

Procedural-Clinical outcomes and definitions

Device success was defined as successful delivery and deployment of the device with the attainment of <30% final residual stenosis, by angiographic visual estimation. Procedure success was defined as device success and no major peri-procedural complications (Emergent CABG, coronary perforation requiring pericardial drainage, residual dissection

impairing vessel flow—TIMI-flow II or less). All deaths were considered cardiac unless an undisputed non-cardiac cause was identified. Target-lesion revascularization (TLR) was defined as clinically driven if at repeat angiography the diameter stenosis was 70%, or if a diameter stenosis 50% was present in association with (i) presence of recurrent angina pectoris, related to the target vessel; (ii) objective signs of ischaemia at rest (ECG changes) or during exercise test, related to the target vessel; and (iii) abnormal results of any functional diagnostic test. Scaffold/stent thrombosis was defined according to the Academic Research Consortium definition.[18]

In BVS patients, first permission to participate in registry was obtained. A questionnaire was sent to all living patients with specific queries on re-hospitalization and cardiovascular events. For patients who suffered an adverse event at another centre, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary.

Statistical analysis

A propensity score matching was performed using a proprietary macro developed and tested for SPSS version 22.0 (SPSS Inc., Chicago, Illinois). First, the program performed a logistic regression to score all patients according to the treatment (BVS vs. EES), using as covariates clinical and procedural parameters: age (years), sex (male/female), cardiogenic shock (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), smoking (yes/no), diabetes mellitus (yes/no), pre-procedure TIMI-flow, culprit vessel. Second, the macro searched and selected the best match case of the EES group for every BVS case according to the absolute value of the difference between the propensity score of BVS and EES cases under consideration. Patients in the 2 groups were matched through a Greedy algorithm based on local optimization.[19] The control selected for a particular case was the one closest to the case in terms of distance. Analyses were then performed on the 2 matched groups (BVS vs. EES), stratified by pairs to account for propensity score matching. For the study, individual data were pooled on a patient-level basis. Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. The student's t test and the chi square test (or Fishers' exact test) were used for comparison of means and percentages. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Kaplan-Meier estimates were compared by means of the log-rank test. For the endpoint MACE, a landmark survival analysis was performed with the landmark time point of 30 days. All statistical tests were two-sided and the P value of < 0.05 was considered statistically significant.

RESULTS

A total of 1306 patients presenting with acute ST-segment elevation myocardial infarction were evaluated for the present analysis (161 patients implanted with BVS and 1145 patients implanted with EES with at least 2-year follow-up available). After matching, 302 patients treated with either BVS or EES (151 patients treated with BVS matched with 151 patients treated with EES) were analysed. Six patients (3.9%) in the BVS group declined to participate in follow-up.

Baseline clinical characteristics were balanced between groups as shown in Table 1.

Table 1 Baseline clinical characteristics

	BVS (N=151)	EES (N=151)	P value
Age, years	56.31 ±10.22	54.90 ±11.52	0.263
Male	109/151 (72.2)	113/151 (74.8)	0.696
Active smoker	71/151 (41.0)	89/151 (58.9)	0.050
Diabetes mellitus	17/151 (11.3)	15/151 (9.9)	0.852
Dyslipidaemia	43/151 (28.4)	41/151 (27.1)	0.226
Hypertension	60/151 (39.7)	56/151 (37.1)	0.723
Family History	51/151 (33.8)	52/151 (34.4)	1.000
Target vessel			0.520
LAD	64/151 (42.4)	62/151 (41.1)	
LCX	32/151 (21.2)	40/151 (26.5)	
RCA	51/151 (33.8)	46/151 (30.5)	
Diagonal	2/151 (1.3)	3/151 (2.0)	
Ramus Intermedius	2/151 (1.3)	0	
Left Main	0	0	
SVG	0	0	

Data are expressed as count and proportion (%) or mean ± standard deviation

A total of 403 devices (193 BVS) were deployed, aspiration thrombectomy was equally performed in the two groups (BVS 76.7% vs 76.8% EES, p=1.000). Pre-dilatation was performed two times more frequently in the BVS group (54.1% vs 28.4%, p<0.001) with a higher balloon / artery ratio (1.02 ± 0.24 vs 0.88 ± 0.21, p=0.002). Post-dilatation was also performed more frequently in the BVS group (and 39.7% vs 21.8%, p<0.001 respectively) but with a balloon / scaffold-stent ratio higher in EES group (1.07 ± 0.09 vs 1.12 ± 0.12, p= 0.031). The rate of post-dilatation increased over time, in the first 75 patients the rate of post-dilatation was 25.3% in the remaining 76 patients was 53.9%. Device success was similar between groups (98.7% vs 99.3%, p=1.000). (Table 2)

Table 2 Procedural characteristics

	BVS (N=151)	EES (N=151)	P value
Aspiration thrombectomy	115/151 (76.7)	116/151 (76.8)	1.000
Pre-dilatation performed	80/151 (54.1)	42/151 (28.4)	<0.001
Pre-dilatation balloon / artery ratio	1.02 ± 0.24	0.88 ± 0.21	0.002
Maximal diameter balloon pre-dilatation, mm	2.54 ± 0.47	2.40 ± 0.48	0.111
Supportive wire used	18/151 (12.2)	3/151 (2.0)	<0.001
Device failure	2/151 (1.5)	1/151 (0.7)	1.000
Device success	149/151 (98.7)	150/151 (99.3)	1.000
Procedure success	148/151 (98.0)	150/151 (99.3)	0.622
Mean scaffold diameter, mm	3.21 ±0.33	3.20 ± 0.46	0.827
Mean total nominal scaffold length, mm	26.32 ± 13.27	27.76 ± 14.81	0.378
Number of scaffolds deployed per treated vessel	1.28 ± 0.61	1.39 ± 0.73	0.148
0	2 (1.3)	0	0.398
1	115 (76.2)	108 (71.5)	
2	25 (16.6)	32 (21.2)	
3	8 (5.3)	7 (4.6)	
4	1 (0.7)	3 (2.0)	
5	0	1(0.7)	
Procedures with overlapping scaffolds, n (%)	31/151 (20.7)	39/151 (25.8)	0.340
Post-dilatation performed	60/151 (39.7)	33/151 (21.8)	<0.001
Post-dilatation balloon / scaffold or stent ratio	1.07 ± 0.09	1.12 ± 0.12	0.031
Maximal post-dilatation balloon diameter, mm	3.45 ± 0.41	3.54 ± 0.59	0.435
Complications occurring anytime during the procedure			
Any dissection	10/151 (6.7)	8/151 (5.3)	0.809
Thrombosis	0	0	
Perforation	1/151 (0.7)	0	

Data are expressed as count and proportion (%)or mean ± standard deviation

Baseline culprit vessels, vessel dimensions, percentage of stenosis, TIMI flow and thrombotic burden were similar between patients treated with BVS and those treated with EES. (Table 3)

At the end of the procedure, there were no cases of TIMI flow 0, and final TIMI 3 flow was achieved in 87.4% and 86.1% of BVS and EES group respectively (p= 0.296) with similar minimal lumen diameter and percentage stenosis.

6-month clinical outcomes Cardiac death was observed in 1.9 vs 2.0, p=0.97; the rate of any myocardial infarction was 5.5% in the BVS group and 1.3% in EES group, p=0.05. Target lesion revascularisation rate was 3.5% and 1.3% respectively, p=0.23. Acute scaffold thrombosis occurred in 2.1% of BVS implanted patients and 0.7% of EES implanted

Table 3 Angiographic characteristics

	BVS (N=151)	EES (N=151)	P value
Pre-procedure			
TIMI flow			0.213
0	80/151 (53.0)	85/151 (56.3)	
1	16/151 (10.6)	12/151 (7.9)	
2	31/151 (20.5)	40/151 (26.5)	
3	24/151 (15.9)	14/151 (9.3)	
Thrombus burden			0.551
1	24/148 (16.2)	20/150 (13.3)	
2	21/148 (14.2)	16/150 (10.7)	
3	12/148 (8.1)	9/150 (6.0)	
4	12/148 (8.1)	18/150 (12.0)	
5	79/148 (53.4)	87/150 (58.0)	
Total thrombotic occlusion			
RVD (mm)	2.76 ± 0.72	2.71 ± 0.47	0.608
Non-total thrombotic occlusion			
RVD (mm)	2.60 ± 0.52	2.72 ± 0.54	0.179
MLD (mm)	0.82 ± 0.46	0.91 ± 0.66	0.335
Diameter stenosis (%)	68.07 ± 15.08	66.27 ± 21.57	0.571
Post-procedure			
TIMI flow			0.296
0	0	0	
1	2/151 (1.3)	0/151	
2	17/151 (11.3)	21/151 (13.9)	
3	132/151 (87.4)	130/151 (86.1)	
RVD (mm)	2.63 ± 0.54	2.98 ± 1.76	0.023
MLD (mm)	2.11 ± 0.50	2.22 ± 0.54	0.067
Diameter stenosis (%)	20.64 ± 11.02	22.28 ± 9.92	0.181
Acute lumen gain	1.98 ± 0.67	2.06 ± 0.73	0.398

Data are expressed as count and percentages or mean ± standard deviation

patients, p=0.29. In both groups Subacute ST rate was 0.7%, p=0.99. Three out of 4 scaffold thromboses occurred in patients without post-dilatation performed at the index procedure. The overall MACE rate 7.6% vs 2.7%, p=0.06. A landmark analysis showed that the 30-day MACE rate in BVS patients without post-dilatation was 6.8% while in patients with post-dilatation was 3.6%.

12-month clinical outcomes From 6 to 12-month follow-up only a target lesion revascularization and one non-target vessel revascularization occurred in the group treated with bioresorbable vascular scaffold.

Table 4 Clinical outcomes

	6-month follow-up			12-month follow-up			18-month follow-up		
	BVS (n = 145)	EES (n = 151)	P value	BVS (n = 145)	EES (n = 151)	P value	BVS (n = 145)	EES (n = 151)	P value
All-cause death (%)	2.1 (3)	2.0 (3)	0.97	2.8 (4)	2.0 (3)	0.68	2.8 (4)	3.0 (4)	0.99
Cardiac	2.1 (3)	1.3 (2)	0.97	2.1 (3)	1.3 (2)	0.63	2.1 (3)	1.3 (2)	0.63
MACE (n.) %	7.6 (11)	2.7 (4)	0.06	8.1 (12)	2.7 (4)	0.03	9.8 (14)	3.6 (5)	0.03
MI (n.) %	5.5 (8)	1.3 (2)	0.05	5.5 (8)	1.3 (2)	0.05	6.3 (9)	2.3 (3)	0.07
TLR (n.) %	3.5 (5)	1.3 (2)	0.23	4.2 (6)	1.3 (2)	0.14	5.7 (8)	1.3 (2)	0.05
Non-TVR (n.) %	2.1 (3)	2.0 (3)	0.97	2.8 (4)	2.0 (3)	0.67	3.6 (5)	4.0 (5)	0.95
Definite ST (n.) %	2.8 (4)	1.3 (2)	0.38	2.8 (4)	1.3 (2)	0.38	4.3 (6)	1.3 (2)	0.15
Acute	2.1 (3)	0.7 (1)	0.29	2.1 (3)	0.7 (1)	0.29	2.1 (3)	0.7 (1)	0.29
Subacute	0.7 (1)	0.7 (1)	0.99	0.7 (1)	0.7 (1)	0.99	0.7 (1)	0.7 (1)	0.99
Late	-	-	-	-	-	-	0.0 (0)	0.0 (0)	-
Very late	-	-	-	-	-	-	1.5 (2)	0.0 (0)	0.18

18-month clinical outcomes From 12 to 18 month 2 very late scaffold thrombosis were observed in the BVS group, at 416 and 449 days after implantation, in both cases the dual antiplatelet therapy was interrupted at the moment of the event. In both cases the review of intravascular imaging showed scaffold malapposition. In the EES group 2 additional non TVR were reported one of them associated with a myocardial infarction.

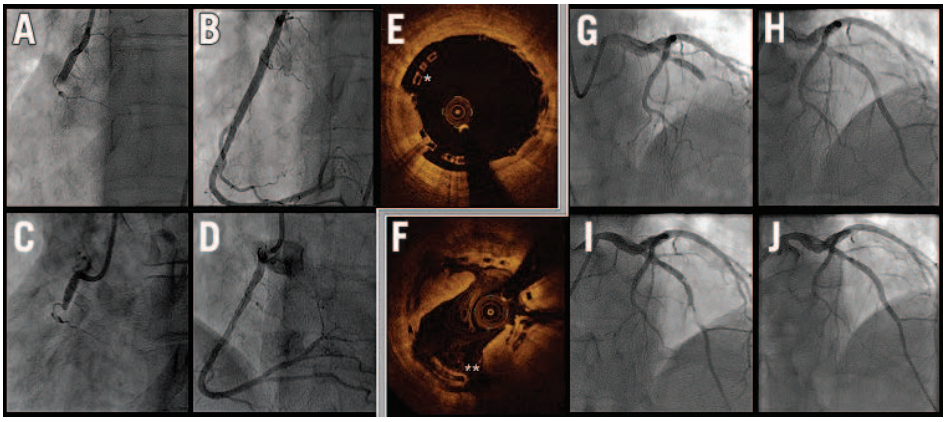

Figure 2 Cases of very late scaffold thrombosis
Both cases were performed with satisfactory final angiographic results. Case 1 (panels A-E): A) baseline; B) final result of the index procedure; C) thrombosis; D) final result of the event treatment. Post-dilatation was performed during the index intervention, but at the end of the procedure intravascular imaging (E) highlighted the remaining malapposition (*). Case 2 (panels F-J): G) baseline; H) final result of the index procedure; I) thrombosis; J) final result of the event treatment. At the time of the event, intravascular imaging (F) showed persistent malapposition (**).

DISCUSSION

The feasibility of BVS implantation in patients presenting with acute myocardial infarction has been recently reported with preliminary information on short-term clinical outcomes.[11-13] However, data comparing the mid-term performance of the bioresorbable technology with the current generation metal DES in this specific subset are limited. The present study represents an early investigation evaluating the use of the second-generation BVS for the treatment of patients presenting with STEMI in comparison with everolimus-eluting metal stents in terms of acute angiographic results and 18-month clinical outcomes.

The majority of the treated patients presented with a TIMI 0 or 1 and more than 60% of the lesions showed a large thrombus burden (4 or 5) in the culprit vessel, in line with what observed in recent large trials on myocardial infarction with minimal exclusion criteria.[20, 21] Such data suggest a patient's population with coronary lesions probably resembling the daily clinical practice in acute myocardial infarction.

Procedural and angiographic data showed an overall comparable device success rate between the two groups, with similar incidence of intra-procedural complication. At the end of the procedure the restoration of TIMI 3 flow was achieved in a high number of patients and similarly in both groups with comparable acute lumen gain, percentage diameter stenosis and minimal lumen diameter.

On the other hand, when analysing the clinical outcomes in the BVS group was observed a higher rate of events at 18-month follow-up with a larger number of TLR and MI an overall higher MACE rate. Although a difference became statistically significant at mid-term follow-up the larger component of such difference is due to events occurred in the very early phase after implantation. In particular three scaffolds thrombosis occurred on day one after implantation.

It should be highlighted that the devices analysed in the present study were used in a period when the post-dilation was not regarded as a key point during the device implantation especially in the acute subset. Studies reporting pooled data from different European registries performed in the same time period of our, showed similar rates of scaffold thrombosis at 30 days.[13]

Our group recognized the relevance of additional high-pressure post-dilation when implanting bioresorbable scaffolds[22] and this translated into a gradual increase in the use of this technique during the inclusion in the present study up the point that the rate of post-dilation was double in the second half of the enrolment compared to the first half.

This concept has been embraced by the scientific community and the current recommendations for BVS implantation suggest the high pressure post-dilatation as an

important action to improve scaffold deployment with a possible beneficial effect on clinical outcomes.[22]

In a later randomized trial, the TROFI II, evaluating short-term imaging results in either BVS or EES in acute myocardial infarction, the rate of subacute scaffold thrombosis was 1.1%. In this study the implantation technique was slightly different from ours, thrombus aspiration was mandatory in every patient with a post-dilation performed in a slightly higher number of cases.[23]

As a matter of fact in our investigation patients without post-dilatation had a higher MACE rate in the first month and both the very late scaffold thrombosis was associated with relevant malapposition. Given this background a possible role of the implantation technique in the occurrence of events cannot be excluded.

The acute myocardial infarction has been classically a field where operators attempted to re-establish the TIMI 3 flow in the culprit vessel reducing at the minimum the amount of manoeuvres, including aggressive post-dilatation, at the lesion site, to minimize the risk of distal embolization. However, a possible association between post-dilation and no-reflow or slow-flow phenomenon currently remains to be clarified[24, 25] and the seminal observation reported in the present study could support a more frequent use of the post-dilatation to optimize scaffold expansion even in acute patients. Large randomized trials currently under preparation may add in further understand on the real performance of bioresorbable technologies in the acute setting.

LIMITATIONS

The number of subject evaluated in the present study is limited and data on clinical outcomes should be considered descriptive and hypothesis generating.

The two study groups were not randomized, despite the use of propensity matching, unadjusted confounders might remain, possibly having an impact on results

Larger patient population and longer follow-up would be needed to adequately compare this novel technology with current generation metal DES.

CONCLUSION

The present study investigated the angiographic and mid-term clinical outcomes in patients treated with either BVS or EES. Implantation of bioresorbable vascular scaffold showed a higher rate of events. Procedural factors might have had a role in these findings and an optimal implantation technique including high pressure post-dilatation should be considered also in the acute setting when using bioresorbable scaffolds.

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Chapter 8

Everolimus-eluting bioresorbable vascular scaffolds implanted in coronary bifurcation lesions: Impact of polymeric wide struts on side-branch impairment

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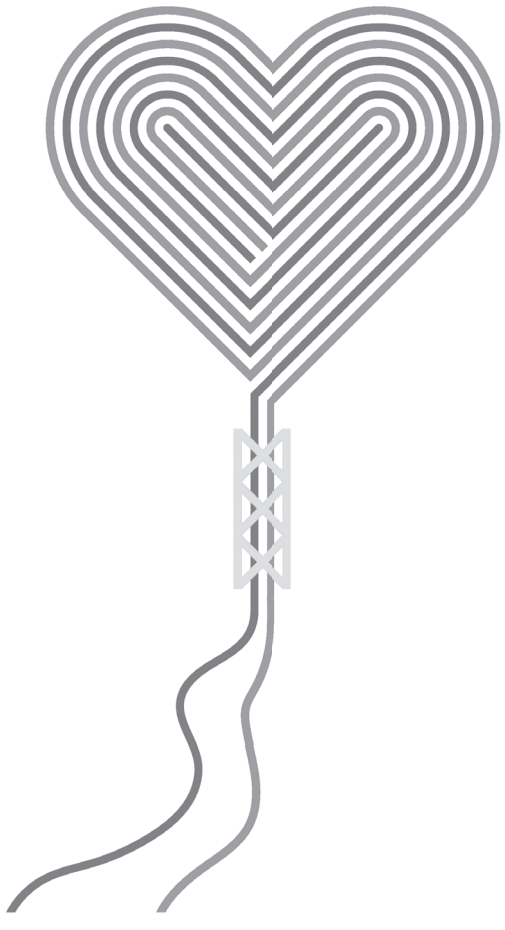

ABSTRACT

Background

Limited data are available on bioresorbable vascular scaffolds (BVS) performance in bifurcations lesions and on the impact of BVS wider struts on side-branch impairment.

Methods

Patients with at least one coronary bifurcation lesion involving a side-branch ≥2 mm in diameter and treated with at least one BVS were examined. Procedural and angiographic data were collected and a dedicated methodology for off-line quantitative coronary angiography (QCA) in bifurcation was applied (eleven-segment model), to assess side-branch impairment occurring any time during the procedure. Two- and three- dimensional QCA were used. Optical coherence tomography (OCT) analysis was performed in a subgroup of patients and long-term clinical outcomes reported.

Results

A total of 102 patients with 107 lesions, were evaluated. Device- and procedural-successes were 99.1% and 94.3%, respectively. Side-branch impairment occurring any time during the procedure was reported in 13 bifurcations (12.1%) and at the end of the procedure in 6.5%. Side-branch minimal lumen diameter (Pre: 1.45 ± 0.41 mm vs Final: 1.48 ± 0.42 mm, p = 0.587) %diameter-stenosis (Pre: 26.93 ± 16.89% vs Final: 27.80 ± 15.57%, p = 0.904) and minimal lumen area (Pre: 1.97 ± 0.89 mm2 vs Final: 2.17 ± 1.09 mm2, p = 0.334), were not significantly affected by BVS implantation. Mean malapposed struts at the bifurcation polygon-of- confluence were 0.63 ± 1.11.

Conclusions

The results of the present investigation suggest feasibility and relative safety of BVS implantation in coronary bifurcations. BVS wide struts have a low impact on side-branch impairment when considering bifurcations with side-branch diameter ≥ 2 mm.

INTRODUCTION

Coronary artery bifurcation treatment is a frequent and challenging subset in interventional cardiology. The introduction of first generation drug eluting stents (DES) was associated with a reduction in main vessel restenosis rate compared with balloon angioplasty or bare metal stent implantation [1,2], but without a clear benefit in terms of side branch ostium impairment and restenosis regardless the technique used [3–5]. Data on second-generation DES, extrapolated from post-hoc analyses of randomized trials are encouraging, with similar long-term mortality after zotarolimus and everolimus DES implantation in bifurcation and non-bifurcation lesions [6]; On the other hand the presence of permanent metallic material at the side-branch ostia could be associated with delayed vascular healing and incomplete neointimal coverage [7] with a possible impact on late thrombotic events [8]. Given this background bioresorbable vascular scaffolds (BVS) could provide a novel paradigm for bifurcation treatment possibly overcoming some of the long-term limitation of metallic DES, avoiding after bioresorption sidebranch ostium caging and long-term malapposition. A possible drawback of the BVS usage in such lesions, could be represented by the theoretical risk of an increased acute side-branch impairment due to the wider BVS struts, as previously hypothesized and demonstrated for very small (b 0.5 mm) side-branches [9]. Despite the presence of recently reported analyses in relatively simple lesions, [10] at the current state of the art, very limited data are available on BVS performance in bi- furcation lesions [11,12] especially when evaluating the impact of BVS implantation on side-branch impairment in vessels with a visually estimated diameter ≥ 2.0 mm. Therefore, we sought to report feasibility, procedural performance and acute angiographic results after BVS implantation in this specific subgroup with a detailed evaluation of side- branch ostium at pre- and post-implantation and describing mid-term clinical outcomes.

Methods

The present report is an investigator initiated, single-arm, single-centre study to assess feasibility and performance of the second- generation everolimus-eluting BVS for the treatment of patients with coronary bifurcation lesions.

Patients eligible for the present analysis were ≥ 18 years of age, presenting with stable angina or acute coronary syndromes with at least one *de novo* bifurcation lesion (regardless of morphology, number, length and angulations), involving a side-branch (SB) ≥ 2 mm by visual estimation in diameter treated with at least one BVS implantation. Exclusion criteria were minimal comprising pregnancy, known intolerance to contrast medium and participation to another investigational drug or device study before reaching the primary endpoints. Procedural details, including materials and techniques were collected. Pre- and post-BVS implantation off-line two-dimensional quantitative

coronary angiography (QCA) and, if technically feasible, off-line three- dimensional-QCA were performed. Optical coherence tomography (OCT) analyses at post-BVS implantation in a subgroup of patients, and clinical long-term clinical outcomes were evaluated. All patients included in the present analyses were part of the bioresorbable vascular scaffold evaluation program at the Thoraxcenter Rotterdam, The Netherlands and were already included in the EXPAND or in the BVS STEMI FIRST study.

Survival status information was obtained from the national population registry. A questionnaire was sent to all living patients with specific queries on re-hospitalization and cardiovascular events. Patients received the questionnaire on planned follow-up (1-, 6-, 12-month follow-up).

For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed.

In case of death all possible events in that specific patient were investigated by reviewing our hospital records and referring hospitals or general practitioner were contacted to collect as much information as possible. In case patients did not send back the questionnaires, a second form was sent by post after one month. If this was not returned, patients were contacted by phone.

Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. The BVS received the CE mark for clinical use, indicated for improving coronary lumen diameter in patients with ischemic heart dis- ease due to *de novo* native coronary artery lesions with no restriction in terms of clinical presentation. Therefore, the BVS can be currently used routinely in Europe in different settings comprising the acute MI without a specific written informed consent in addition to the standard informed consent to the procedure. Given this background, a waiver from the hospital Ethical Committee was obtained for written informed consent, as according to Dutch law writ- ten consent is not required, if patients are not subject to acts other than as part of their regular treatment.

Study procedure

The procedures were performed according to standard practice. The device implantation was performed in accordance with the manufacturer's recommendations, at a rate of 2 atm per 5 s up to burst pressure. Pre- and post-dilatation were encouraged but not mandatory. Wiring of the side-branch before main vessel stenting was per- formed at the operator's discretion and mainly based on the extension of the disease and anatomical characteristics. A single scaffold approach was encouraged as preferred approach

for the majority of cases. Side- branch treatment was recommended only in cases with side-branch impairment or significant atherosclerotic disease. After the procedure, dual antiplatelet therapy was recommended for at least one year followed by aspirin indefinitely.

Definitions

Device success was defined as the attainment of a residual final stenosis b 30% in Main vessel (MV) or side-branch (SB) segment covered by BVS. Procedural success was defined as device success and no major peri-procedural complications (emergent CABG, coronary perforation requiring pericardial drainage, residual dissection impairing vessel flow with final TIMI-flow grade ≤ 2 in MV or SB). Clinical success was defined as procedural success and no in-hospital major adverse cardiac events (MACEs). All deaths were considered cardiac unless an undisputed non-cardiac cause was identified. Myocardial infarction (MI) and scaffold thrombosis were defined according to the Academic Research Consortium definition. Any target bifurcation revascularization was de- fined as clinically driven if at repeat angiography a diameter stenosis N 70% was observed, or if a diameter stenosis N 50% was present in the main vessel or in the daughter branches in association with 1) recurrent angina pectoris; 2) objective signs of ischemia (electrocardiogram changes) at rest or during exercise test, likely to be related to the target vessel; 3) abnormal results of any invasive functional diagnostic test. The target bifurcation failure was defined as the composite of cardiac death, target vessel myocardial infarction, or clinically-driven target bi- furcation revascularization. MACEs were defined as the composite of cardiac death, any re-infarction (Q or Non Q-Wave) or clinically- driven target bifurcation revascularization.

To investigate the BVS performance in MV/SB ostium, we adopted the following procedural and angiographic parameters already reported in de the literature [7]:

"Side-branch impairment", as previously described [7] and defined as a composite of 1) SB TIMI flow grade b 3 after MV stenting, 2) need of guidewire(s) different from the default wire to rewire SB after MV stenting, 3) failure to rewire the SB after MV stenting, or 4) failure to dilate the SB after MV stenting and SB rewiring; "SB acute angiographic result", defined as the comparison between the pre- and the post-procedure 2-dimensional QCA–estimated minimal lumen diameter of 3-mm ostial SB sub-segment, according to the modified eleven-segment model analysis [13–15].

Study device

The second-generation everolimus-eluting BVS (ABSORB; Abbott Vascular, Santa Clara, CA, USA) consist of a backbone of semi crystalline polymer of poly-L-lactide acid, an amorphous matrix of poly-DL-lactide acid which controls the everolimus release (100 micrograms/cm2) and two markers of platinum at proximal and distal edges of scaf-

fold which are radiopaque and facilitate the correct implantation of device. The entire polymer is degraded to carbon dioxide and water.

Quantitative coronary angiography analysis

Off-line quantitative coronary angiography (QCA) analysis was per- formed using the Cardiovascular Angiography Analysis System (CAAS; Version 5.10, Pie Medical Imaging, Maastricht, the Netherlands) soft- ware packages, according to methodological standards previously de- scribed and adopting the modified- eleven-segment model [13–15]. Only matched pre- and post-BVS implantation projections were considered for the analyses. Two-dimensional QCA (2DQCA) was performed using the angiographic image with the largest distal bifurcation angle. 3-dimensional QCA (3DQCA) was performed if at least two projections had been acquired at least 30° apart; The following parameters were included: reference vessel diameter (RVD), minimal lumen diameter (MLD) and percentage diameter stenosis (%DS) of MV, SB and 3-mm ostial SB sub-segment (segment 8 in the eleven segment model), bifurcation proximal angle (between proximal MV and SB) and bifurcation distal angle (between distal MV and SB). If 3DQCA was feasible, minimal lumen area and percentage area stenosis of MV, SB and 3-mm ostial SB sub-segment were added (Fig. 1). Bifurcation lesions were classified ac- cording to the Medina classification; AHA/ACC modified lesion criteria, extent of coronary disease, presence of calcification, lesion length, SB and main vessel (MV) thrombolysis in myocardial infarction (TIMI)- flow grade.

Optical coherence tomography image acquisition and analysis

Intravascular imaging was encouraged but not mandatory and left to the operator discretion. The Optical coherence tomography (OCT) ex- amination was performed with the Illumien or Illumien Optis systems and the corresponding Dragonfly or Dragonfly Duo intravascular imaging catheters (St. Jude Medical, St. Paul, MN, USA). The catheter was advanced into the MV distally to the treated segment and then automated pullback (20 mm/s) and simultaneous contrast injection (flush rate 3– 4 mL/s) were performed to acquire the images. Off-line analysis of the OCT images was performed using the QCU-CMS software (Medis Medical Imaging System, Leiden, The Netherlands) at 1-mm longitudinal intervals within the treated coronary segment, including proximal and distal 5-mm edge segments, after exclusion of frames with b 75% lumen contour visibility, using previously described methodology for the analysis of bioresorbable scaffolds [16]. Morphometric measurements were performed as previously described, using the abluminal strut points for the delineation of the scaffold contour. A scaffold strut was defined as incompletely apposed when there was no contact between the abluminal border of the strut and the vessel wall. This definition does not include struts located in front of SBs ostia which were defined as SB-related struts and were recorded

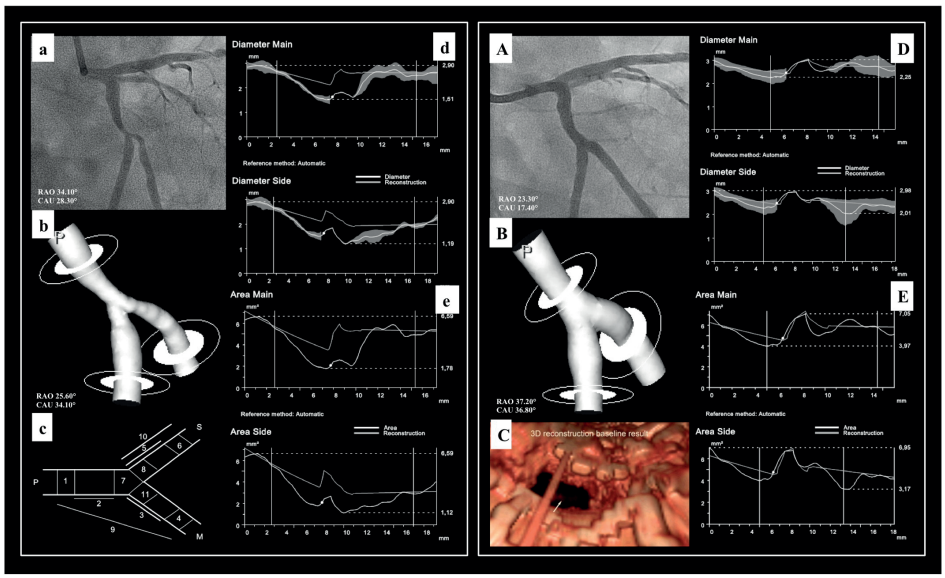

Figure 1 Quantitative coronary analysis and 3-dimensional reconstruction.
A. Pre-procedural angiogram of treated bifurcation was acquired at RAO34.10°CAU28.30° and LAO51.30°CAU29.70° (not shown). b. 3-dimensional reconstruction is shown in the optimal projection (P = proximal main vessel). c. 11-segment model in Cardiovascular Angiography Analysis System (CAAS); P, M and S = proximal main vessel, distal main vessel and side branch, respectively. d and e. Pre-procedural reference vessel diameter and area curve, respectively, for proximal main vessel into distal main vessel and side branch. A. Post-procedural angiogram. B and C. 3-dimensional reconstruction using 3dimensional-QCA and 3-dimensional OCT, respectively (white arrow indicates SB ostium). D and E. Post-procedural reference vessel diameter and area curve, for proximal main vessel into distal main vessel and side branch.

separately. The bifurcation of interest was identified in the OCT pullback and divided in 3 sub- segments: proximal, polygon of confluence and distal (Fig. 2). Strut apposition was calculated separately for each of the sub-segments.

Statistical analysis

Continuous variables were expressed as mean and standard deviation or as median and interquartile ranges if data were non-normally distributed. Dichotomous variables are presented as count and/or percentages. The paired *t*-test was used for comparison between pre and post-procedure QCA parameters. Statistical analysis was performed using SPSS, version 20.0 for Windows (SPSS Inc., Chicago, IL, US).

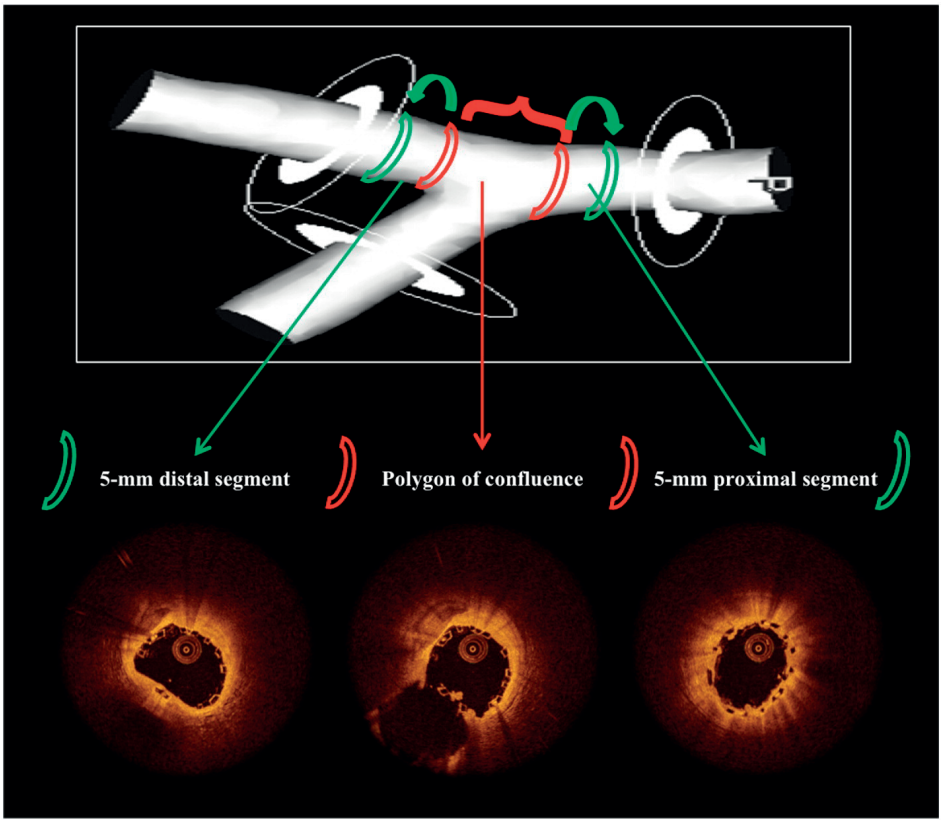

Figure 2 Subsegments location in the treated bifurcation lesion.
The bifurcation of interest was identified in the OCT pullback and divided in 3 sub-segments: we defined the polygon of confluence as the sub-segment between the last (distally) and the first (proximally) cross sections (red lines) in which the contort was not distorted by the side branch. The distal and proximal sub-segments (green lines) were defined as the 5-mm distal and the 5-mm proximal sub-segments from the last and the first cross sections of the polygon of confluence, respectively.

RESULTS

A total of 102 patients, with 107 bifurcation lesions, were included in this study. The baseline clinical characteristics are reported in Table 1. Briefly, the average age was 59.61 ± 10.79 years, 81.4% of the patients were male, 43.9% showed a multivessel disease, 57.8% were admitted with an acute coronary syndrome and approximately one third of these acute patients presented with ST-segment elevation myocardial infarction (Table 1).

Table 1. Baseline Clinical Characteristics

Patient characteristics	N = 102
Age, yrs	59.61 ± 10.79
Gender (male)	83 (81.4)
Risk factors	
Family History of CAD	30 (29.4)
Diabetes mellitus	16 (15.7)
Hypercholesterolemia	53 (52.0)
Hypertension	57 (55.9)
Active smoking	42 (41.2)
Kidney disease	6 (5.9)
Clinical history	
Previous MI	23 (22.5)
Previous PCI	15 (14.7)
Previous CABG	2 (2.0)
Previous TIA/stroke	4 (3.9)
Peripheral arterial disease	7 (6.9)
Chronic obstructive pulmonary disease	5 (4.9)
Extent of coronary artery disease	
Single vessel disease	60 (56.1)
2-vessel disease	40 (37.4)
3-vessel disease	6 (5.6)
Left main	1 (0.9)
Clinical presentation	
Acute coronary syndrome	59 (57.8)
STEMI	19 (18.6)
Acute heart failure	2 (2.0)
Out-hospital cardiac arrest	2 (2.0)

Values are expressed as mean ± standard deviation (SD) or count (n) and percentages (%). *CABG* = coronary artery by-pass; *CAD* = coronary artery disease; *MI* = myocardial infarction; *PCI* = percutaneous coronary intervention; *STEMI* = ST-segment elevation myocardial infarction; *TIA* = transient ischemic attack;

Angiographic and procedural characteristics

Angiographic characteristics of bifurcation lesions (N = 107) are listed in Table 2. The most frequently treated lesion was on left anterior descending/diagonal bifurcation (68.2%), a large part of the lesions involved both the main branch and the side-branch (true bifurcation lesions 42.0%), moderate or severe calcification was present in nearly one third of the lesions (28.9%) and long lesions were commonly observed (55.1%). In 10 cases (9.3%) the bifurcation was located in chronically occluded coronary segments.

Table 2 Angiographic Characteristics

Number of Bifurcations	N = 107
Target bifurcation	
Distal left main	2 (1.9)
Left anterior descending/Diagonal	73 (68.2)
Circumflex/Marginal	26 (24.3)
Right posterior descending/posterior lateral	6 (5.6)
ACC/AHA modified lesion classification	
Type B2	73 (68.2)
Type C	34 (31.8)
True bifurcations	45 (42.0)
Moderate or severe calcification	31 (28.9)
Length lesion > 20 mm	59 (55.1)
Chronic total occlusion	10 (9.3)
Medina bifurcation classification	
1.1.1	20 (18.7)
1.1.0	24 (22.4)
1.0.1	11 (10.3)
0.1.1	14 (13.1)
1.0.0	14 (13.1)
0.1.0	18 (16.8)
0.0.1	6 (5.6)
MV TIMI flow pre-procedure	
0	13 (12.1)
1	4 (3.7)
2	3 (2.8)
3	87 (81.3)
SB TIMI flow pre-procedure	
0	9 (8.4)
1	4 (3.7)
2	2 (1.9)
3	92 (85.9)

Values are expressed as count (n) and percentages (%).
ACC/AHA = American College of Cardiology/American Heart Association; MV = main vessel; SB = side branch; TIMI = thrombolysis in myocardial infarction.

Reflecting the presence of acute patients TIMI flow 0 or 1 pre- intervention was reported in 17 main vessel lesions (15.9%) and with a similar rate in the side-branch (Table 2).

The most commonly performed technique was the provisional one scaffold approach (93.4%). A crossover from a one-scaffold to two- scaffolds technique occurred in only one case.

Pre-dilation was highly recommended and performed in 84.1% of the main vessels and 23.4% of the side-branches before treatment.

Side-branch wire protection before provisional scaffolding was per- formed in 38.0% of the cases, in 41 cases (38.3%) a highly supportive wire (Hi-Torque Balance Heavy-weight or Hi-Torque Whisper ES) was the default for wiring the MV or the SB (MV 32.7%, SB 9.3%).

One-hundred and seventy-eight Absorb BVS were implanted, with a maximum scaffolded length of 102 mm (4 BVS). To achieve an optimal final angiographic result, the MV post-dilation was performed in 64 cases (59.8%), non-compliant balloons were frequently used (52/64, 81.2%) and a proximal optimization technique (POT) was performed in the 59.4% of overall post-dilations.

SB ostium dilation across MV scaffold struts was performed in 39 bifurcations (36.4%), using balloons with mean diameter of 2.03 mm ± 0.48 and semi-compliant in the 99% of cases (Table 3).

Table 3 Procedural Characteristics

Number of bifurcations	N = 107
Technique	
Provisional	100 (93.4)
T-stenting	5 (4.7)
Culotte	1 (0.9)
Mini-crush	1 (0.9)
MV direct stenting	14 (13.1)
MV pre-dilation	90 (84.1)
Semi-compliant balloon	82 (76.6)
Non-compliant balloon	17 (15.9)
SB wiring before MV provisional stenting	38 (38.0)*
Default supportive wire	41 (38.3)
MV supportive wire	35 (32.7)
SB supportive wire	10 (9.3)
Cutting balloon	1 (0.9)
Rotablator	2 (1.9)
SB ostium dilation before MV treatment	25 (23.4)
Total number of scaffolds	178
Mean scaffolds per-bifurcation	1.66 ± 0.84

Table 3 Procedural Characteristics (*continued*)

Number of bifurcations	N = 107
MV Scaffold	104 (97.2)
Scaffold diameter (mm)	3.03 ± 0.4
Scaffold length (mm)	19.95 ± 5.6
SB Scaffold	14 (13.1)
Scaffold diameter (mm)	2.8 ± 0.3
Scaffold length (mm)	16.21 ± 4.8
MV post-dilation	64 (59.8)
Semi-compliant balloon	17 (15.9)
Non-compliant balloon	52 (48.5)
POT	38 (35.5)
Final kissing balloon inflation	5 (4.6)
SB ostium dilation after MV stent	39 (36.4)
Balloon diameter (mm)	2.03 ± 0.48
Vascular access	
Radial	66 (61.7)
Femoral	42 (39.2)
Contrast media (ml)	208.15 ± 90.82

Values are expressed as mean ± standard deviation (SD) or count (n) and percentages (%). ∗ % calculated over all provisional approach.
MV = main vessel; POT = Proximal Optimization Technique; SB = side branch.

The device success was achieved in 99.1% of the cases (106/107), in one calcified lesion a residual final stenosis not inferior to 30% persisted at the end of the procedure. The procedural success was 94.3%, in one case, a distal edge dissection caused a post-procedure MV TIMI flow grade equal to 1 and in 4 cases the final SB TIMI flow grade was inferior to 3 (TIMI flow 0 in one case, after MV provisional approach without a previous SB wiring). The "SB impairments" occurred in 13 procedures (12.1%). The most frequently reported cause was a SB TIMI flow grade b 3 after MV scaffolding, reported in 10 cases. In 6 of those cases the final SB TIMI flow grade improved after SB ostium post-dilatation, with no need for SB treatment (Table 4).

Quantitative coronary angiography analysis

Two-dimensional and 3-dimensional QCA were performed in 103 patients and 40 patients, respectively (inadequate views either pre- or post- procedure were excluded).

At the end of the procedure, the side-branch was not significantly affected by the BVS implantation the main vessels. In the 2-dimensional and the 3-dimensional QCA analyses, there were no differences between the pre- and post-procedure reference vessel diameter (2D RVD: 1.98 ± 0.33 mm vs 2.03 ± 0.41 mm, p = 0.718 - 3D RVD: 2.00 ± 0.28

Table 4 Procedural results

Number of bifurcations	N = 107
Device success	106 (99.1)
Procedural succes	101 (94.3)
Final MV TIMI flow grade 3	106 (99.1)
Final SB TIMI flow grade 3	103 (96.3)
SB impairment	13 (12.1)
SB TIMI flow grade < 3 after MV stenting	10 (9.3)
SB TIMI flow grade =0 after MV stenting	4 (3.7)
SB TIMI flow grade =1 after MV stenting	2 (1.9)
SB TIMI flow grade =2 after MV stenting	4 (3.7)
Need to guidewire(s) different from the default wire to rewire SB after MV stenting	5 (4.7)
Failure to rewire the SB after MV stenting	1 (0.9)
Failure to dilate the SB after MV stenting	1 (0.9)

Values are expressed as count (n) and percentages (%).
MV = main vessel; SB = side branch; TIMI = thrombolysis in myocardial infarction.

mm vs 2.08 ± 0.34 mm, p = 0.28), minimal lumen diameter (2D MLD: 1.45 ± 0.41 mm vs 1.48 ± 0.42 mm, p= 0.587 - 3D MLD: 1.54 ± 0.37 mm vs 1.61 ± 0.41 mm, p = 0.363), and minimal lumen area (3D MLA 1.97 ± 0.89 mm2 vs 2.17 ± 1.09 mm2, p = 0.334). In true bifurcation lesions the (2D) diameter stenosis appeared significant- ly increased (%DS pre PCI 58.7% vs 31.9%, p = 0.0001) after treatment. Additionally, also in the 3-mm ostial SB sub-segment, no statistically significant pre- and post-procedural variations were reported in terms of reference vessel diameter (2D RVD: 1.99 ± 0.33 mm vs 2.06 ± 0.38 mm, p = 0.309 - 3D RVD: 2.03 ± 0.28 mm vs 2.10 ± 0.32 mm, p = 0.123), minimal lumen diameter (2D MLD: 1.51 ± 0.38 mm vs 1.53 ± 0.44 mm, p = 0.567 - 3D MLD: 1.59 ± 0.35 mm vs 1.62 ± 0.41 mm, p = 0.760) minimal lumen area (3D MLA 2.10 ± 0.86 mm2 vs 2.19 ± 1.10 mm2, p = 0.660) (Tables 5 and 6).

Optical coherence tomography findings

OCT imaging was performed in 20 bifurcations after BVS implantation (Table 7). Incomplete scaffold apposition (ISA) was observed in 15 patients, with a mean ISA area of 0.12 ± 0.14 mm2 and a mean percentage of malapposed struts per patient equal to 3.87 ± 4.12%.

The sub-segments analysis was available in 19 cases (one case was excluded owing to incomplete pullback of treated MV). The mean percentages of malapposed struts per patient in distal, polygon of confluence and proximal sub-segments were 1.50 ± 2.59%, 4.08 ± 9.45% and 6.41 ± 16.99% respectively.

Table 5 Pre- and post-procedural vessel diameters 2D-QCA-evaluation

Number of bifurcations	Pre-PCI (N=103)	Post-PCI (N=103)	p value
Main vessel			
Reference diameter (mm)	2.63 ± 0.61	2.77 ± 0.55	0.286
Minimal lumen diameter (mm)	1.30 ± 0.55	2.35 ± 0.52	<0.001
% diameter stenosis	50.13 ± 18.86	15.14 ± 8.40	<0.001
Side branch			
Reference diameter (mm)	1.98 ± 0.33	2.03 ± 0.41	0.718
Minimal lumen diameter (mm)	1.45 ± 0.41	1.48 ± 0.42	0.587
% diameter stenosis	26.93 ± 16.89	27.80 ± 15.57	0.904
3-mm ostial side branch sub-segment			
Reference diameter (mm)	1.99 ± 0.33	2.06 ± 0.38	0.309
Minimal lumen diameter (mm)	1.51 ± 0.38	1.53 ± 0.44	0.567
% diameter stenosis	23.97 ± 15.99	25.82 ± 16.15	0.697
Angle			
Proximal Main Vessel/Side Branch (°)	143.58 ± 17.44	143.53 ± 18.04	0.282
Distal Main Vessel/Side Branch (°)	53.47 ± 15.65	52.68 ± 17.95	0.764

Values are expressed as mean ± SD. PCI = percutaneous coronary intervention.

Table 6 Pre- and post-procedural vessels diameters and areas 3DQCA-evaluation

Number of bifurcations	Pre-PCI (N=40)	Post-PCI (N=40)	p value
Main vessel			
Reference diameter (mm)	2.60 ± 0.72	2.77 ± 0.48	0.128
Minimal lumen diameter (mm)	1.48 ± 0.59	2.43 ± 0.46	<0.001
Minimal lumen area (mm^2)	1.99 ± 1.52	4.81 ± 1.70	<0.001
Percentage area stenosis	63.47 ± 21.49	22.15 ± 12.27	<0.001
Side branch			
Reference diameter (mm)	2.00 ± 0.28	2.08 ± 0.34	0.280
Minimal lumen diameter (mm)	1.54 ± 0.37	1.61 ± 0.41	0.363
Minimal lumen area (mm^2)	1.97 ± 0.89	2.17 ± 1.09	0.334
Percentage area stenosis	42.25 ± 21.50	38.62 ± 21.33	0.305
3-mm ostial side branch sub-segment			
Reference diameter (mm)	2.03 ± 0.28	2.10 ± 0.32	0.123
Minimal lumen diameter (mm)	1.59 ± 0.35	1.62 ± 0.41	0.760
Minimal lumen area (mm^2)	2.10 ± 0.86	2.19 ± 1.10	0.660
Percentage area stenosis	34.98 ± 19.98	37.48 ± 20.28	0.798
Angle			
Proximal Main Vessel/Side Branch (°)	139.19 ± 15.94	140.86 ± 14.70	0.597
Distal Main Vessel/Side Branch (°)	59.02 ± 12.31	55.23 ± 13.34	0.189
Proximal Main Vessel/Distal Main Vessel (°)	152.40 ± 13.08	155.74 ± 10.27	0.128

Values are expressed as mean ± SD. PCI = percutaneous coronary intervention.

Table 7 Optical coherence tomography (OCT) analysis post-scaffold implantation in bifurcated coronary lesions

OCT variables	N = 20
In-segment analysis	
Minimum lumen area (mm^2)	5.05 ± 1.05
Mean lumen area (mm^2)	7.36 ± 1.37
Lumen volume (mm^3)	231.49 ± 97.72
Minimum scaffold area (mm^2)	5.68 ± 1.08
Mean scaffold area (mm^2)	7.61 ± 1.45
Scaffold volume (mm^3)	236.88 ± 99.71
Mean ISA area (mm^2)	0.12 ± 0.14
Max ISA area (mm^2)	1.64 ± 1.56
% ISA area	1.71 ± 2.22
Mean prolapse area (mm^2)	0.47 ± 0.27
Max prolapsed area (mm^2)	1.40 ± 0.75
% prolapse	6.27 ± 3.46
Distal dissection (N = 15)	5 (33.3)
Proximal dissection (N = 17)	4 (23.5)
Analyzed struts per patient	292 ± 117.52
Malapposed struts per patient	10.15 ± 8.37
% malapposed struts	3.87 ± 4.12
Side branch struts per bifurcation	3.20 ± 2.31
5-mm proximal MV sub-segment (N = 19)	
Malapposed struts	2.11 ± 4.53
% malapposed struts	6.41 ± 16.99
Polygon of confluence (POC) (N = 19)	
Malapposed struts	0.63 ± 1.11
% malapposed struts	4.08 ± 9.45
SB-related struts	2.0 ± 2.13
5-mm distal MV sub-segment (N = 19)	
Malapposed struts	0.61 ± 1.09
% malapposed struts	1.50 ± 2.59

Values are expressed as mean ± SD, median [IQR] or n (%). ISA = incomplete scaffold apposition. MV = main vessel. OCT = optical coherence tomography. POC = polygon of confluence.

Table 8 Clinical outcomes at 1-year follow-up.

Clinical events	N = 102
Major adverse cardiac events	5.5%
All cause death	2.2%
Cardiac death	1.1%
Myocardial infarction	4.4%
Target lesion revascularization	3.3%
Target vessel revascularization	6.6%
Non- target vessel revascularization	3.4%
Scaffold thrombosis	3.3%
Definite ST	2.2%
Probable ST	0.0%
Possible ST	1.1%

ST scaffold thrombosis

In the sub-group of patients in which a proximal optimization technique (POT) was performed, the percentages of malapposed struts in the polygon of confluence and in the proximal sub-segment were numerically lower compared with the sub-group in which POT was not performed (1.54 ± 3.42% vs 6.37 ± 12.49% and 3.31 ± 3.57% vs 8.33 ± 24.29% respectively).

Clinical outcomes

Survival status was available in 99.0% (101/102). The overall mortality at one year was 2.2% (2/101). Clinical follow-up rate was 91.1% (92/101) with a median follow up duration of 731 days (interquartile range, IQR: 644–762 days). 89 patients had a follow-up of at least one year (2 patients had a follow-up duration of 353 and 332 days respectively. One patient was lost to follow-up with follow-up duration of 202 days).

The remaining 9 out of 101 patients could not be approached for clinical follow-up the cause was refusal to participate and in one case emigration. A total of 5 patients were reported to have major adverse cardiac event (Fig. 4) including 1 cardiac death (and possible ST), 4 MI (2 ST-segment elevation MI, one peri-procedural MI caused by a distal scaffold dissection and one occurred after a staged procedure on a non-target vessel, and 2 non-ST elevation MI, both due to a late scaffold thrombosis(Table 8), 3 ischemia-driven target bifurcation revascularizations (due to an in-scaffold restenosis inducing angina). At one year, 2 cases of definite ST (at day 47 and at day 142) occurred. (See Table 9).

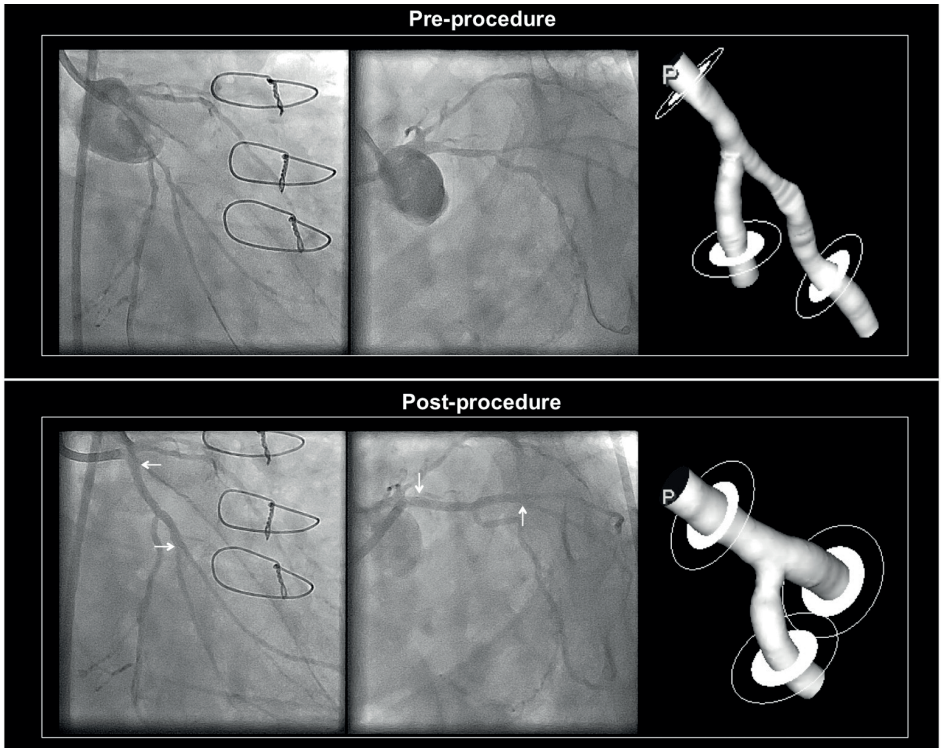

Figure 3 Treatment of a coronary bifurcation located in a diffusely disease vessel in a patient with previous coronary artery bypass graft.
In the upper panel angiographic appearance pre-intervention and 3-dimentional QCA reconstruction of the target bifurcation. In the lower panel post-procedure appearance and 3-dimentional QCA reconstruction with no side-branch impairment.

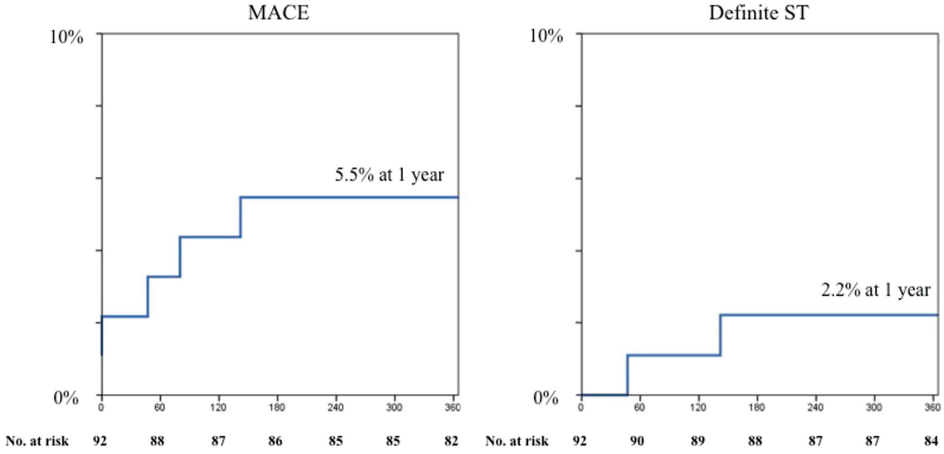

Figure 4 Kaplan–Meier curves for MACE and scaffold thrombosis.
MACE: major adverse cardiac events; ST: scaffold thrombosis

Table 9 Cases of definite scaffold thrombosis

Case #	Type of lesion	Technique	Device size (mm)	Timing (days from index procedure to scaffold thrombosis)	Dual antiplatelet therapy at the time of scaffold thrombosis
1	LAD/1°Diagonal Medina 1.1.1 Angulation 78°	"Provisional MV stenting"	3.0 x 18	142	ASA (80 mg) + PRASUGREL (10 mg)
2	LAD/1°Diagonal CTO	"Provisional MV stenting"	3.0 x 28 3.5 x 18 3.5 x 18 (2 overlap)	47	ASA (80 mg) + CLOPIDOGREL (75 mg)

ASA = aspirin; *CTO* = chronic total occlusion; *LAD* = left anterior descending; *MV* = main vessel.

DISCUSSION

Initial clinical experience with bioresorbable vascular scaffolds has been focused on simple lesions and relatively stable patients. Recent data, mainly derived from registry, provided additional information on safety, feasibility and performance of BVS in more complex lesions and patients [17,18], however specific challenging subsets such as bifurcation lesions remain poorly investigated.

In the present study we reported the BVS performance after implantation in bifurcation lesions in wide range clinical scenarios, including patients presenting with acute myocardial infarction or showing multivessel disease (Fig. 3) and coronary chronic total occlusions.

The approach adopted in the vast majority of the cases was a T-provisional scaffolding, a solid amount of evidence suggests this strategy as to be the preferable in most of the bifurcation cases [19,20]. Such evidences are provided from studies performed with metal stents but it is reasonable to apply the same principles to bioresorbable devices, especially considering the fact that a single scaffold technique reduce the amount of polymer at the bifurcation site, avoids overlap and the need for multiple layer of polymer.

The scaffold sizing in bifurcation lesions could be challenging in case of remarkable vessel tapering distally to the side-branch.

Recently Ishibashi et al. reported that oversizing the implanted scaffold compared to both the proximal and distal vascular maximal diameter (Dmax) could be associated with clinical events. On the other hand underexpansion was also shown to increase the risk of scaffold thrombosis [21]. Probably a reasonable approach could be to balance the proximal and distal Dmax, ensuring optimal apposition proximally after post-dilatation, without causing high vessel stretch and injury distally.

In the present series, the size of the BVS was usually chosen on the basis of the proximal maximal diameter (Dmax) [22] but also taking into account the distal Dmax, often performing low-pressure deployment and thereafter performing proximal optimization.

In our report we observed a trend toward a reduction in malapposition at the proximal segment and at the polygon of confluence in the cases with performed proximal optimization.

Taking into consideration the faith of the side-branches after BVS implantation, an initial concern associated with the larger BVS struts width and its possible impact on side-branch impairment has been raised [9]. Maramatsu et al. performed a post-hoc analysis of the ABSORB-EXTEND and SPIRIT First and II Trials [9] to assess the incidence of small SB occlusion (bifurcation lesions involving a SB b 2 mm) after either BVS or everolimus-eluting metal stents. BVS demonstrated a higher incidence of post-procedural side branch occlusion compared with EES but only in small side branches with a reference vessel diameter ≤ 0.5 mm.

To investigate the impact of BVS wider struts on side-branch impairment when treating what is most commonly considered a bifurcation lesion (with a side-branch of at least 2 mm in diameter) [20,23–27], we performed a detailed analysis taking into consideration both procedural and angiographic parameters.

We evaluated the composite parameter of "side-branch impairment" observing the TIMI flow, need for dedicated wires, or failure to re-cross or dilate the side-branch and we assessed the 2- and 3- dimensional QCA pre and post BVS implantation of the side-branch.

A side-branch impairment occurred in 13 cases (12.1%) after BVS deployment, the most frequently reported cause was a SB TIMI flow grade b 3 after MV scaffolding, (10 cases). Of note in 6 of those cases the final SB TIMI flow grade improved to grade TIMI flow 3 after SB ostium post-dilation, with no need for SB treatment and reducing the occurrence of final side-branch slow flow to only 4 bifurcations (3.7%). Such data are in line with previous investigations evaluating the impact of first- and second-generation drug eluting metal stents on side-branch impairment [7].

It would therefore appear that the concern of an increased side- branch damage or occlusion after BVS implantation may not be justified, when considering side-branches with a visually estimated diameter of 2 mm or more.

The OCT analysis although performed in a subgroup of patients showed a low amount of malapposition in the overall bifurcation segment probably also in association with a high rate of post-dilatation. Malapposition was distributed with a reduction from the proximal to the distal segment of the bifurcation, highlighting the possible need for proximal optimization.

Finally, although due to the small number of patients and events re- ported is not possible to reach firm conclusions in terms of clinical outcomes, the overall mortality and the MACE rate suggest a relative safety of BVS implantation in bifurcation lesions given a preferred single scaffold technique and a high rate of pre and post dilatation.

LIMITATIONS

The present report is an investigator initiated, single center, single arm study and is a retrospective analysis of the BVS evaluation program at Thoraxcenter Rotterdam, The Netherlands. The choice for BVS implantation was left to operator discretion; this could be source of selection bias. The absence of a comparator arm is limiting the interpretation of our data. In the present study side branch vessel with a visual estimated diameter ≥ 2.0 mm was evaluated, by QCA the mean RVD of the side branch was 1.98 mm highlighting the well-known underestimation of vessel size by QCA. Intravascular imaging was encouraged but not mandatory and left to the operator discretion, such approach could be associated with selection bias. The limited number of patients does not allow reaching firm conclusions in terms of clinical outcomes, therefore clinical data should be considered as purely descriptive and hypothesis generating.

CONCLUSION

The present investigation suggest the feasibility and good performance of everolimus-eluting BVS implantation in patients with a native bifurcated coronary lesion, involving a SB ≥ 2 mm in diameter. Further investigations in randomized clinical trials are required to provide the actual impact of this novel technology on safety, efficacy and long- term clinical outcomes, also compared to second-generation DESs.

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Chapter 9

Impact of calcium on procedural and clinical outcomes in lesions treated with bioresorbable vascular scaffolds - a prospective BRS registry study

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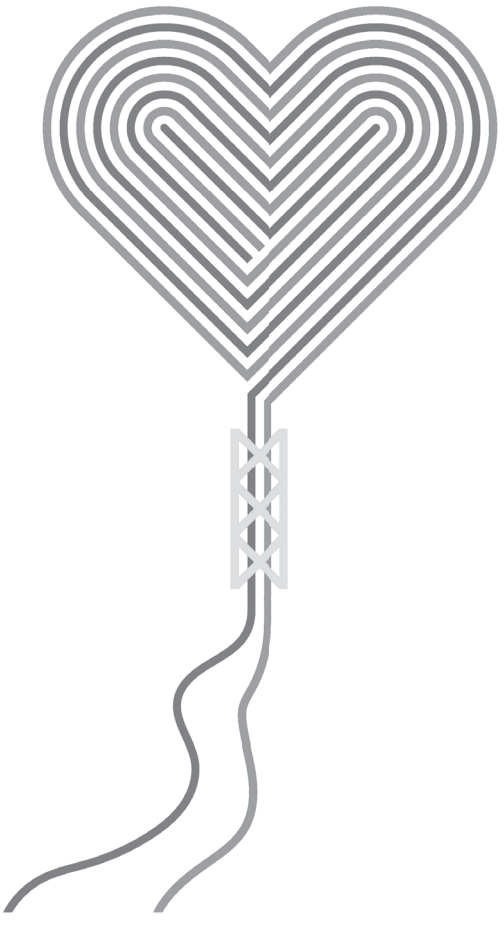

ABSTRACT

Background

There is limited data on the impact of calcium (Ca) on acute procedural and clinical outcomes in patients with lesions treated with bioresorbable vascular scaffolds (BRS). We sought to evaluate the effect of calcium on procedural and clinical outcomes in a 'real world' population.

Methods

Clinical outcomes were compared between patients with at least 1 moderately or heavily calcified lesion (Ca) and patients with no/mild calcified lesions (non-Ca) enrolled in our institutional BRS registry.

Results

455 patients (N) with 548 lesions (L) treated with 735 BRS were studied. Patients in the Ca group (N=160, L=200) had more complex (AHA B2/C lesion: 69.0% in Ca vs 14.9% in non-Ca, $p < 0.001$) and significantly longer lesions (27.80 ±15.27 vs 19.48 ±9.92mm, $p<0.001$). Overall device success rate was 99.1% with no significant differences between the groups. Despite more aggressive lesion preparation and post-dilatation compared to non Ca, acute lumen gain was significantly less in Ca lesions (1.50 ±0.66 vs 1.62 ±0.69mm, $p= 0.040$) with lower final MLD (2.28± 0.41 vs 2.36±0.43, $p=0.046$). There were no significant differences in all-cause mortality, total definite scaffold thrombosis (ST), target lesion revascularization and myocardial infarction between the 2 groups. Late ST was more frequent in the Ca group compared to non Ca group (Late ST: 2.1 vs 0%, $p=0.02$).

Conclusions

Clinical outcomes after BRS implantation in calcified and non-calcified lesions were similar. A remarkable difference in timing of thrombosis was observed, with an increased rate of late thrombosis in calcified lesions.

Condensed Abstract

Clinical outcomes were compared between patients with at least 1 moderately or heavily calcified lesion (Ca) and patients with no/mild calcified lesions (non-Ca) enrolled in our institutional BRS registry. 455 patients with 548 lesions treated with 735 BRS were studied. More aggressive lesion preparation, post-dilatation and the use of intracoronary imaging were more likely encountered in Ca lesions. There was a significant increase in late ST in patients with Ca lesions compared to patients with non-Ca lesions treated with BRS. However there were no significant differences in all-cause mortality and MACE between the groups.

INTRODUCTION

Bioresorbable scaffolds (BRS) have been developed as an alternative to metallic stents as the need for mechanical support for the treated vessel is temporary, and beyond the first few months there are potential disadvantages of a permanent metallic prosthesis. In earlier studies to demonstrate Absorb BRS feasibility and safety, severe calcification was an exclusion criterium [1-6]. Calcified lesions may be challenging and encountered in up to 35% of patients who undergo percutaneous coronary intervention (PCI) [7-8]. Lesion calcification has been associated with increased PCI complexity with worse procedural outcomes compared to non-calcified lesions [9]. Wire crossing, delivery of equipment during pre and post dilation and stent delivery may be more cumbersome. In calcific lesions, the effect of acute plaque recoil may affect stent expansion and is associated with adverse clinical and angiographic outcomes [10-11]. Currently there is still limited data on the impact of calcium (Ca) on acute procedural and clinical outcomes in patients with lesions treated with BRS. We sought to determine the impact of calcification on acute angiographic and 2 year clinical outcomes of a large cohort of patients treated solely with the Absorb Bioresorbable Vascular Scaffold (BVS) system (Abbott Vascular, Santa Clara, CA, USA).

METHODS

This is an investigator-initiated, prospective, single-center, single-arm study evaluating performance of the Absorb BVS in lesions representative of daily clinical practice, including calcified lesions, total occlusions, long lesions and small vessels [12-13]. The study inclusion period was from September 2012 till January 2015. Inclusion criteria were patients presenting with STEMI [12], NSTEMI, stable/ unstable angina, or silent ischemia caused by a *de novo* stenotic lesion in a native previously untreated coronary artery [13]. Procedural and long-term clinical outcomes were assessed. The primary endpoint was major adverse cardiac events, defined as a composite of cardiac death, myocardial infarction and target lesion revascularization.

Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC, and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. Approval of the ethical board of the Erasmus MC was obtained. All patients undergoing clinical follow-up provided written informed consent for the PCI and to be contacted regularly during the follow-up period of the study.

Quantitative Coronary Analysis (QCA)

The angiographic analysis was performed by three independent investigators. Coronary angiograms were analyzed with the CAAS 5.10 QCA software (Pie Medical BV, Maastricht, the Netherlands). The QCA (Quantitative Coronary Analysis) measurements provided reference vessel diameter (RVD), percentage diameter stenosis and minimal lumen diameter (MLD). Acute gain was defined as post-procedural MLD minus pre-procedural MLD (in an occluded vessel MLD value was zero by default).

Angiographic Assessment of Lesion Calcification

Lesion calcification was recognized as radio-opacities within the vessel wall at the treated lesion. Calcification was categorized as either none/mild or moderate if the radio-opacities were noted only during the cardiac cycle before contrast injection and further classified as either none/mild or moderate based on visual assessment. Severe calcification was defined as having multiple persisting (that are noted even without cardiac motion) opacifications of the coronary wall and visible in more than one projection, surrounding the complete lumen of the coronary artery at the site of the lesion) as per SYNTAX definition (www.syntaxscore.com). Angiographic assessment of calcification was conducted independently by 2 cardiologists. In cases of disagreement, a third independent cardiologist reviewed the films and provided a final diagnosis.

Follow-up

Clinical demographic data of all patients were obtained from municipal civil registries. Follow-up information specific for hospitalization and cardiovascular events was obtained through questionnaires. If needed, medical records or discharge letters from other hospitals were requested. Events were adjudicated by an independent clinical events committee (CEC). All information concerning baseline characteristics and follow-up was gathered in a clinical data management system. Only patients who had given written consent for follow up were included in the clinical outcome assessments.

Definitions

The primary endpoint was major adverse cardiovascular events (MACE), defined as the composite endpoint of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). The secondary endpoints were device oriented composite endpoints (DOCE: composite of cardiac death, target vessel myocardial infarct and clinically indicated target lesion revascularization) and patient oriented composite endpoints (POCE: composite of all-cause mortality, all-cause myocardial infarct and any revascularization). Deaths were considered cardiac unless a non-cardiac cause was definitely identified. TLR was described as any repeated revascularization of the target lesion. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or

surgical bypass of any segment of the target vessel. Non-target vessel revascularization was described as any revascularization in a vessel other than the target lesion. Scaffold thrombosis (ST) and MI were classified according to the Academic Research Consortium (ARC). [1] Clinical device success was defined as successful delivery and deployment of the first study scaffold/ stent at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-scaffold/ stent residual stenosis of < 30% as evaluated by QCA. Clinical procedure success was described as device success without major peri-procedural complications or in-hospital MACE (maximum of 7 days).

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. , A cox regression was performed to investigate clinical outcomes at two years, with the binary variable calcification (yes/ no). Adjusted cox regression were performed using fourteen patient and lesion factors (See Online supplement Table 1) to account for baseline differences between patients with at least 1 moderately or heavily calcified lesion (Ca) and patients with no/mild calcified lesions (non-Ca). Statistical analyses were performed using SPSS, version 21 (IL, US). All statistical tests were two-sided and the P value of < 0.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics are shown in Table 1A. A total of 548 lesions in 455 patients were studied of which 200 (36.5%) lesions in 160 patients (35.2%) were moderately or heavily calcified (Ca group). (Table 1A). Patients in the Ca group were older, with more hypertension, and kidney disease. In the calcified cohort, there were 1.24 lesions per patient. Lesion and QCA characteristics are as shown in Table 1B. The left anterior

Table 1A Demographic Characteristics

	BRS (N= 455)		
	Patients with at least 1 calcified lesion (N= 160/35.2%)	Patients with no calcified lesions (N=295/64.8%)	
Age	62.12 ± 10.64	56.54 ± 10.25	<0.001
Male	122/160 (76.3)	220/295 (74.6)	0.734
Ex/Active smoker*	81/160 (50.7)	181/294(61.6)	
Diabetes mellitus	31/160 (19.4)	40/295 (13.6)	0.107

Table 1A Demographic Characteristics (*continued*)

	BRS (N= 455)		
	Patients with at least 1 calcified lesion (N= 160/35.2%)	Patients with no calcified lesions (N=295/64.8%)	
Dyslipidaemia*	75/158 (47.5)	109/288 (37.8)	0.056
Hypertension	93/159 (58.5)	139/290 (47.9)	0.038
Family History	55/160 (34.4)	127/295 (43.1)	0.206
CVA/TIA	13/160(8.1)	16/295 (5.4)	0.260
Prior MI	26/160 (16.3)	27/295 (9.2)	0.032
Prior PCI	10/160 (6.3)	20/295 (6.8)	1.000
Prior CABG	1/160 (0.6)	0	0.352
Kidney disease	11/160 (6.9)	8/295 (2.7)	0.048
Heart failure	7/160 (4.4)	7/295 (2.4)	0.262
Clinical presentation			0.002
Stable Angina	53/160 (33.1)	63/ 295 (21.4)	
Unstable Angina	14/160 (8.8)	32/295 (10.8)	
STEMI	40/160 (25.0)	118/295 (40.0)	
NSTEMI	51/160 (31.9)	82/295 (27.8)	
CCF	2/160 (1.3)	0	
Disease Involvement			0.060
SVD	97/160 (60.6)	210/295 (71.2)	
DVD	42/160 (26.3)	63/295 (21.4)	
TVD	21/160 (13.1)	22/295 (7.4)	

Values are expressed in numbers (percentages) or mean ± standard deviation when appropriate.

Table 1B Lesion Characteristics

	BRS (L = 548)		
	Calcified Lesions (L=200/36.5%)	Non Calcified Lesions (L=348/ 63.5%)	P value
Target vessel			
LAD	126/200 (63.0)	128/348 (36.8)	<0.001
LCX	27/200 (13.5)	96/348 (27.6)	<0.001
RCA	42/200 (21.0)	111/348(31.9)	0.007
Diagonal	4/200 (2.0)	13/348(3.7)	0.314
Ramus	0	0	-
Left Main	1/200 (0.5)	0	0.365
SVG	0	0	-
Lesion AHA			
A	5/200 (2.5)	71/348 (20.4)	< 0.001
B1	60/200 (30.0)	226/348 (64.9)	< 0.001
B2	85/200 (42.5)	46/348 (13.2)	< 0.001
C	53/200 (26.5)	6/348 (1.7)	<0.001

Table 1B Lesion Characteristics (*continued*)

	BRS (L = 548)		
	Calcified Lesions (L=200/36.5%)	Non Calcified Lesions (L=348/ 63.5%)	P value
Bifurcation	61/199 (31.7)	58/347 (16.7)	<0.001
CTO	13/200 (6.5)	4/348 (1.1)	0.001
Mod/Heavy calcification	133/67	0	
TIMI			
Preprocedure			0.074
TIMI 0	35/200 (17.5)	87/344 (25.0)	
TIMI 1	6/200 (3.0)	17/344 (4.9)	
TIMI 2	50/200 (14.4)	50/344 (14.4)	
TIMI 3	125/200 (62.5)	190/344 (54.6)	
QCA Analysis			
Pre-procedure			
Treatment length	27.80 ± 15.27	19.48 ± 9.92	<0.001
RVD (mm)	2.52±0.57	2.62 ± 0.57	0.053
MLD (mm)	0.85±0.47	0.75±0.55	0.036
Diameter stenosis (%)	65.39±18.68	70.78±20.98	0.004

Values are expressed in numbers (percentages) or mean ± standard deviation when appropriate.

descending artery (n=254, 46.4%) was the most commonly treated vessel in the study population. Lesions in the Ca group were more complex (AHA B2/C lesion: 69.0% in Ca vs 14.9% in non-Ca, $p < 0.001$) and significantly longer. Compared to non-Ca group, lesions in the Ca groups had smaller RVD and lower percentage diameter stenosis.

Procedural characteristics are as shown in Table 1C. Ca lesions were treated with more aggressive lesion preparation compared to non Ca as evidenced by the more significant use of pre-dilatation, rotational atherectomy and scoring balloon. The use of buddy wires was higher in Ca lesions compared to non Ca lesions. Figure 1A illustrates the satisfactory expansion with minimal eccentricity on OCT of a calcified LAD treated with a BRS. Figures 1B and 1C illustrates the acute and 2 year angiographic and IVUS result respectively after rotational atherectomy and lesion preparation followed by BRS implantation in a calcified coronary artery. A total of 735 scaffolds were implanted in the study population with more scaffolds per lesion for Ca lesions (1.58 vs 1.21). Scaffold diameter was similar in the two groups however scaffold length implanted was longer in the Ca group. Post-dilatation was more frequently used in the Ca group (Ca vs non Ca: 64.8% vs 42.1%, $p<0.001$).

Table 1C Procedural Characteristics

		BRS (L = 548)		
		Calcified Lesions (L=200/36.5%)	Non Calcified Lesions (L=348/ 63.5%)	P value
Number of treated lesions per procedure		1.24 ± 0.48	1.17 ± 0.48	0.133
Aspiration thrombectomy		34/200 (17.1)	106/348 (30.5)	0.001
Rotablation		11/200 (5.5)	0/348	0.002
Scoring balloon		9/200 (4.5)	1/348 (0.3)	0.001
Intracoronary imaging				
	IVUS	30/199 (15.1)	30/348 (8.6)	0.023
	OCT	62/200 (31.0)	95/348 (27.3)	0.378
Pre-dilation		177/200 (88.5)	265/348 (76.1)	<0.001
Max pre-dilation diameter		2.66 ± 0.36	2.53 ± 0.42	0.002
Pre-dilation balloon: artery ratio		1.08 ± 0.25	1.01 ± 0.23	0.005
Maximum pre-dilation inflation pressure, atm		14.25 ± 3.35	13.56 ± 3.01	0.067
Buddy wire		23/199 (11.6)	22/347 (6.3)	0.036
Additional daughter catheter		3/199 (1.5)	3/348 (0.9)	0.673
Mean number of scaffolds		1.58 ± 0.823	1.21 ± 0.53	<0.001
Number of scaffolds (total 735)		315	420	<0.001
	0	1/200 (0.5)	1/348 (0.3)	
	1	117/200 (58.5)	289/348 (83.0)	
	2	56/200 (28.0)	47/348 (13.5)	
	3	18/200 (9.0)	7/348 (2.0)	
	4	8/200 (4.0)	4/348 (1.1)	
Scaffold diameter, mm		3.11 ± 0.32	3.12 ± 0.38	0.615
Scaffold length implanted, mm		34.65± 19.94	23.84 ± 12.20	< 0.001
Overlapping scaffolds		80/200 (40.0)	52/348 (15.0)	<0.001
Maximum scaffold implantation pressure, atm		14.99 ± 1.88	14.86 ± 1.97	0.510
Post-dilatation		129/199 (64.8)	146/347 (42.1)	<0.001
Post-dilatation balloon: mean scaffold diameter ratio		1.06 ± 0.15	1.07 ± 0.10	0.422
Max post-dilatation balloon		3.31 ± 0.43	3.31 ± 0.44	0.906
Maximum post-dilatation inflation pressure, atm		16.27 ± 3.63	15.83 ± 3.97	0.496

Values are expressed as numbers (percentages) or mean ± standard deviation when appropriate.

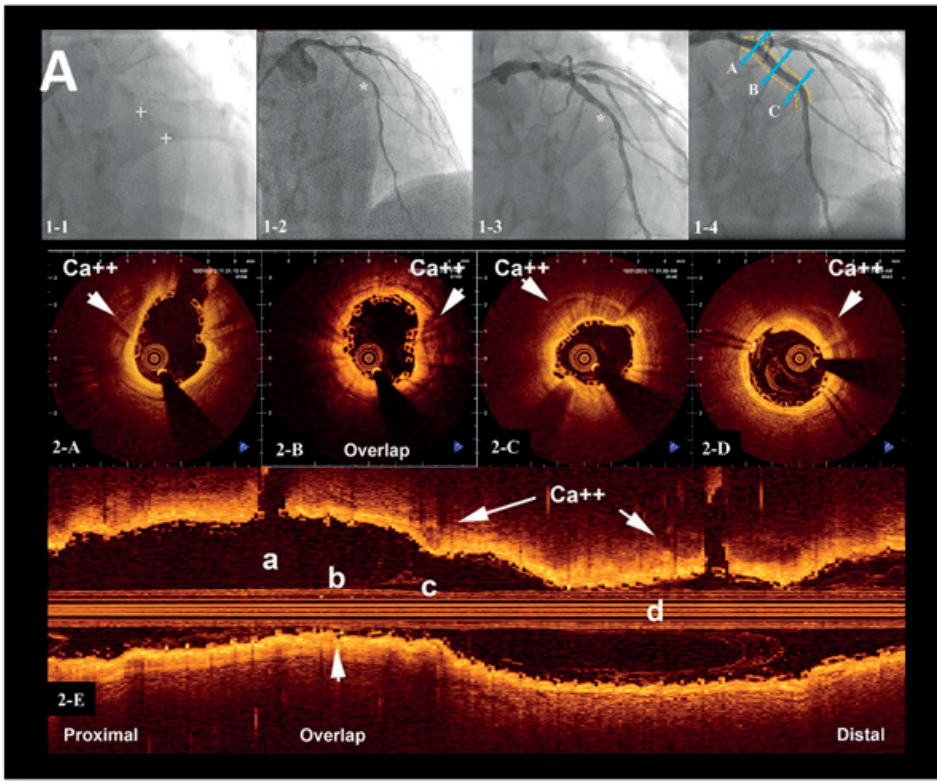

Figure 1A Implantation of Bioresorbable vascular scaffold (BRS in calcified left anterior descending artery (LAD).

Implantation of Bioresorbable vascular scaffolds (Two 3.0 x 28mm Absorb™ BVS deployed in an overlapping manner- indicated in yellow) in a calcified left anterior descending artery (LAD). Calcification marked '+' in Panel 1-1. Target lesion marked '*' preprocedure (Panel 1-2), after predilation with a 2.5mm balloon at (Panel 1-3) and after postdilation with a noncompliant 3.0mm balloon at high pressure (Panel 1-4). Panel 2A-E: Final OCT performed showed that the scaffold was well expanded and apposed with no significant dissection seen. Proximal and distal reference areas were 7.21mm^2 and 5.52mm^2 respectively. The minimal lumen area (MLA) was 4.5mm^2 (2.83 x 1.81mm) with an eccentricity index (EI) of 0.63. Panel 2-A-C showed the corresponding segments of the treated vessel in Panel 1-4. Panel 2-D showed the BRS implanted in a calcified segment of the treated vessel with satisfactory expansion with minimal eccentricity. Panel 2-E showed the longitudinal pullback of the treated vessel.

Procedural outcomes are shown in Table 2A. Post procedure, acute lumen gain was significantly less in Ca compared to non-Ca lesions (1.50 ±0.66 vs 1.62 ±0.69mm, p= 0.040) with lower final MLD (2.28± 0.41 vs 2.36±0.43, p=0.046). RVD and percentage diameter stenosis were smaller in the Ca group compared to the non Ca group though the differences did not reach statistical significance. Procedural success was high for both patient groups (98.7 and 99.7%, p=0.25). Overall device success rate and final TIMI 3 flow result were similar in the two groups.

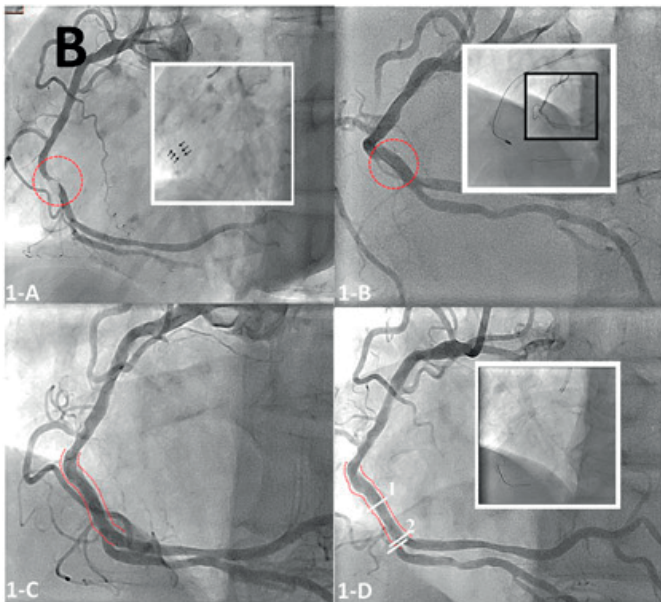

Figure 1B Angiogram and intravascular ultrasound (IVUS) of the right coronary artery (RCA).
Angiogram and intravascular ultrasound (IVUS) of the right coronary artery (RCA). Panel 1-A shows the pre-procedural angiogram at baseline with a severely tight lesion (circled) in the mid segment of the RCA which is heavily calcified (see insert). Panel 1-B shows the RCA post rotational artherectomy with 1.5 mm burr (see insert) and predilation with a Trek NC 3.25 mm balloon. Panel 1-C shows the RCA after deployment of a BRS (BVS Absorb 3.0 × 28 mm - outlined in red). The borderline lesions in the ostium and mid right posterior descending artery (RPDA) was managed conservatively (white arrow). Panel 1-D shows the RCA at 2 years follow up which demonstrates that the previously deployed scaffold in the mid RCA was still widely patent with no significant restenosis (outlined red).

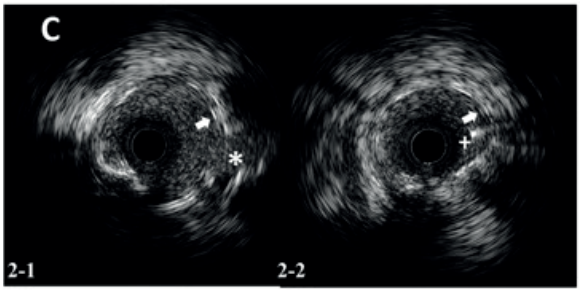

Figure 1C IVUS images of the RCA.
The figure shows IVUS images of the corresponding segments of the RCA in Fig. 1B Panel 1-D at 2 years follow up demonstrating that the scaffold struts (white arrow) remained visible in the mid RCA with good apposition and expansion with side branch (*-RPDA) patency and confirmed the scaffolded vessel remained widely patent with no significant restenosis (Panels 2-1 and 2-2). + - Guidewire.

Table 2A Procedural Outcomes

	BRS (L = 548)		
	Calcified Lesions (L=200/36.5%)	Non-Calcified Lesions (L=348/63.5%)	P value
TIMI post-procedure			0.850
TIMI 0	0	0	
TIMI 1	1/200 (0.5)	2/348 (0.6)	
TIMI 2	12/200 (6.0)	17/348 (4.9)	
TIMI 3	187/200 (93.5)	329/348 (94.5)	
QCA analysis post-procedure			
RVD (mm)	2.75±0.48	2.78±0.45	0.401
MLD (mm)	2.28± 0.41	2.36±0.43	0.046
Diameter stenosis (%)	16.71±8.89	15.30±8.61	0.069
Acute lumen gain	1.50±0.66	1.62±0.69	0.040
Procedural outcomes			
Device success	197/200 (98.5)	346/348 (99.4)	0.208
Bailout by scaffold	6/200 (3.0)	5/348 (1.4)	0.439
Bailout by metallic stent	4/200 (2.0)	5/348 (1.4)	0.547
Intra-procedural thrombosis	1/200 (0.5)	1/348 (0.3)	1.000
Significant dissection	14/200 (7.0)	16/348 (4.6)	0.444
Significant no reflow/ slow flow	9/200 (4.5)	9/348 (2.6)	0.272

MLD minimal lumen diameter; *RVD* reference vessel diameter. Values are expressed as numbers (percentages) or mean ± standard deviation when appropriate.

We were able to obtain written consent for the follow up program in 395 patients (86.8%). Clinical outcomes were available in all (100%) of these patients. (Table 2B). These patient had similar baseline and procedural characteristics as the total population. Kaplan-Meier curves for MACE were parallel throughout the follow-up to two year (Figure 2A). Crude cumulative event rates at two years for the secondary endpoints, described as Kaplan-Meier estimates are as shown in Table 2B. There was a slight trend for higher events on cardiac death and all-cause mortality for patients with calcified lesions. No difference was observed in POCE and DOCE. Though definite ST rates were similar between the two groups (Figure 2B), there was a remarkable variation in acute and late definite ST. For acute definite ST, the incidence was higher in the non-Ca lesions; for late definite ST there was a significant increase in Ca group compared to non-Ca group (Late ST: 2.1% vs 0, p=0.02) but not for very late ST (Table 2B). After adjusting for difference in baseline characteristics, Ca lesions was not found to be a significant predictor of any clinical events (Table 3C).

Table 2B Clinical endpoints at two years, described as Kaplan-Meier estimates

	Calc (n=143)	No-calc (n=252)	P value
MACE (%)	11.7 (17)	8.0 (19)	0.351
DOCE (%)	9.0 (12)	7.3 (17)	0.564
Cardiac death (%)	3.8 (5)	0.8 (2)	0.052
Target Vessel MI	5.3 (7)	5.1 (12)	0.945
Clinically indicated TLR (%)	4.7 (6)	5.9 (14)	0.544
Definite ST (%)	2.1 (3)	2.4 (6)	0.856
Acute	0.0	1.2 (3)	0.191
Subacute	0.0	0.4 (1)	0.450
Late	*2.1 (3)*	*0.0*	0.020
Very late	0.0	0.8 (2)	0.287
Probable ST (%)	0.7 (1)	0.4 (1)	0.682
Acute	0.0	0.0	
Subacute	0.0	0.0	
Late	0.7 (1)	0.4 (1)	0.682
Very late	0.0	0.0	
Definite/ Probable ST (%)	2.9 (4)	2.8 (7)	0.993
Acute	0.0	1.2 (3)	0.191
Subacute	0.0	0.4 (1)	0.450
Late	2.9 (4)	0.4 (1)	0.039
Very late	0.0	0.8 (2)	0.287
POCE (%)	12.2 (23)	17.2 (29)	0.211
All-cause mortality (%)	3.8 (6)	0.8 (3)	0.052
Any revascularization	12.2 (16)	10.3 (25)	0.714
TVR (%)	5.3 (7)	6.5 (16)	0.544
Non-TVR (%)	7.7 (10)	4.7 (11)	0.260
All cause MI (%)	8.3 (11)	6.5 (15)	0.509

DOCE device oriented composite endpoints (Composite of cardiac death, target vessel myocardial infarct and clinically indicated target lesion revascularization); *POCE* patient oriented composite endpoints (Composite of all- cause mortality, all cause myocardial infarct and any revascularization). (Number of composite endpoints does not add up as any patient may have multiple events.)

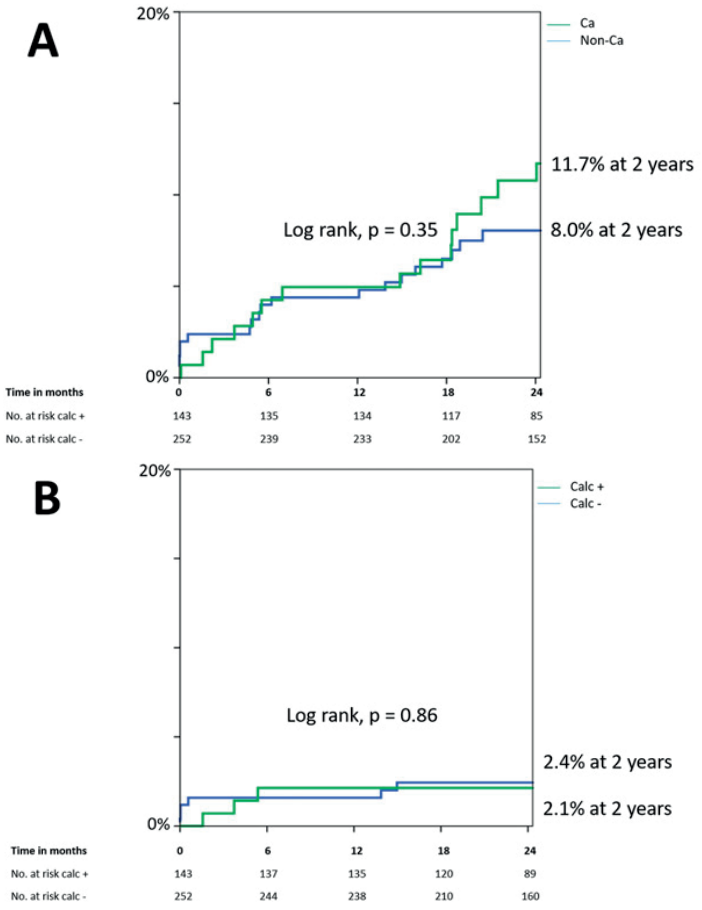

Figure 2 Kaplan-Meier curve showing no significant difference in A) MACE and B) definite ST at 2 years in patients with calcified (Ca) and non-calcified (non-Ca) lesions treated with bioresorbable vascular scaffolds (BRS).

The primary endpoint was major adverse cardiovascular events (MACE), defined as the composite endpoint of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR). Of note while the incidence of acute ST was higher in the non-Ca group compared to Ca group, there was a significant increase in late ST in calcified lesions compared to non-Ca lesions. ST- Scaffold thrombosis.

Table 2C Predictors for clinical outcomes at two years follow-up (using Cox regression), calc vs no calc

		Unadjusted HR (95% CI)	p-value	Adjusted* HR(95% CI)	p value
All-cause death					
	Calc vs non-calc	4.428 (0.859 – 22.822)	0.075	1.7 (0.263 – 10.994)	0.578
Cardiac death					
	Calc vs non-calc	4.428 (0.859 – 22.822)	0.075	1.7 (0.263 – 10.994)	0.578
MACE					
	Calc vs non-calc	1.378 (0.700 – 2.712)	0.353	0.850 (0.382 – 1.895)	0.692
MI					
	Calc vs non-calc	1.393 (0.632 – 3.068)	0.411	0.944 (0.366 – 2.433)	0.905
TLR					
	Calc vs non-calc	0.754 (0.290 – 1.963)	0.564	0.644 (0.225 – 1.845)	0.644
TVR					
	Calc vs non-calc	0.762 (0.314 – 1.853)	0.549	0.629 (0.236 – 1.674)	0.353
Non-TVR					
	Calc vs non-calc	1.627 (0.691 – 3.831)	0.265	0.950 (0.342 – 2.634)	0.921
Definite ScT					
	Calc vs non-calc	0.880 (0.220 – 3.518)	0.856	0.930 (0.206 – 4.234)	0.930
Probable ScT					
	Calc vs non-calc	1.771 (0.111 – 28.307)	0.686	0.917 (0.039 -21.720)	0.957
Def/ Prob ScT					
	Calc vs non-calc	1.005 (0.294 – 3.434)	0.993	0.935(0.242- 3.610)	0.922
DOCE					
	Calc vs non-calc	1.242 (0.593 – 2.600)	0.566	0.961 (0.416- 2.218)	0.926
POCE					
	Calc vs non-calc	1.416 (0.819 – 2.448)	0.213	1.045 (0.556 – 1.963)	0.891

*Adjusted for gender, age, presentation with ACS, multivessel disease, diabetes mellitus, dyslipidemia, smoking, hypertension, peripheral artery disease, small vessel, bifurcation, average scaffold diameter per patient, total scaffold length per patient (See Data supplement for tabulation of propensity score).

DISCUSSION

In our study, the key finding was that despite Ca lesions were more complex, required more lesion preparation, and encountered more deliverability issues with lower acute luminal gain and smaller final MLD, acute procedural and 24 month clinical outcomes were similar regardless of the calcification group with the exception of a higher rate of late ST at 2 years in the Ca group compared to non-Ca group. While there have been earlier studies evaluating the use of BRS in calcified lesions. [16-18], this is the first large clinical prospective registry study involving BRS scaffolds that look at the impact of lesion calcification on long term clinical outcomes at 2 years.

Our findings, which showed that Ca lesions were more complex and required more careful and elaborate lesion preparation including rotational atherectomy (in 5.5% of the lesions), were consistent with similar findings published elsewhere [9, 19]. The use of intracoronary imaging like IVUS was also increased in Ca lesions compared to non Ca lesions. The more frequent use of buddy wires in the Ca group suggested that difficult deliverability issues may be encountered more commonly in Ca lesions thus potentially prolonging procedure times. Despite the advances in interventional techniques, calcific lesions still pose a challenge for the procedurist. Due to their inherent polymeric structural composition and increased strut thickness, BRS have been shown to have less favourable mechanical characteristics including less deliverability and radial strength compared to current second generation DES [19-20]. There have been concerns as to whether such mechanical characteristics may result in less optimal stent performance which may be more pronounced in calcified lesions where focal areas of calcification limit expansion of the BRS more compared to DES [19]. This may have practical clinical implications since suboptimal stent expansions has been known to contribute to metallic stent failure [21] and there have been reports of inadequate scaffold expansion in BRS failure [22-3].

Our findings are also consistent with clinical [24-5] data addressing the feasibility of BRS in calcified lesions. In a recent study looking at specific procedural outcomes in 62 calcified lesions by Panoulas et al [24], expansion of BRS as measured in terms of lumen gain on QCA and intravascular ultrasound (IVUS) was similar between calcified and non-calcified lesions. Acute luminal gain (1.83±0.6 vs. 1.86±0.6mm, p=0.732) and angiographic success were similar (98% non-calcific vs. 95.2% calcific, p=0.369), whereas procedural success was reduced in patients with calcific lesions (94.1% vs. 83.9%, p=0.034) due to higher rates of periprocedural myocardial infarction (MI) (5% vs. 13.1%, p=0.067). MACE rates (10.9% non-calcific vs. 12.9% calcific, p log-rank=0.546) were similar in the median follow-up time of 14 months. However a greater degree of lesion preparation in calcified lesions was also required. OCT was not used and a comparison of the expansion of BRS compared with DES was not performed. In our study, we report 2 year clinical outcomes in a larger study population which showed MACE rates were similar between Ca and non-Ca groups. In another study conducted by Kawamoto et al [25], though eccentric calcium distribution resulted in asymmetric expansion of BRS, the final MSA was still comparable irrespective of calcium distribution, and the use of IVUS for scaffold optimization led to favorable clinical outcomes even in calcified lesions. Earlier OCT findings published from our centre [26] also suggest that regardless of the degree of angiographic calcification, BRS can achieve a similar expansion as DES, in the context of an imaging-guided strategy with adequate lesion preparation. Our findings were also consistent with recent published literature showing that the presence of moderate or severe lesion calcification does not negatively affect angiographic outcomes at both

post-procedure and 13-month follow-up after BVS implantation [27]. However, in this study [27], heavily calcified lesions or those requiring extensive lesion preparation such as rotational atherectomy were excluded according to the study protocol wheras our study included "all comers" lesions with various degrees of calcification or that require rotational atherectomy.

However, BRS deployment requires more lesion preparation and decalcification strategy particularly for moderately or heavily calcified lesions. Further studies are needed to ascertain if in such lesions the use of such a strategy may impact on long term clinical outcomes such as increased TLR rates such as seen in DES deployment after lesion debulking or decalcification using rotational atherectomy [28, 29]. In addition, the postdilation rate reported in our study (Table 1C) was comparable to other studies considering that systematic postdilation was implemented on average in less than 50% of previously published studies [30]. It is still debatable if pursuing a systematic postdilation strategy will have an impact on long term results particularly the risk of very late ST (VLST). Given the results of this study, an analysis of BRS specific implantation technique such as PSP (Prepare the lesion to be reengineered; Size the vessel appropriately; Postdilate to embed scaffold struts into the vessel wall) would be timely and of interest [31].Though the lesions treated in the Ca group were more complex, requiring longer and more overlapping scaffolds and the post dilatation rate of 64.8% was considered relatively low for calcific lesions, the procedural and clinical results were still similar between the Ca and non Ca groups. This may be reassuring since the current practice suggest a large use of postdilation especially in stable patients with complex lesions.

BRS offers several unique potential advantages over DES. The future bioresorption of BRS permits potential future grafting of treated segments, allows potential reopening of "jailed" side branches and potential recovery of vasomotor function and vessel remodeling. These benefits would be more pertinent in patients with calcific lesions, who often have widespread disease resulting in long stented segments. However whether these will translate into long term clinical benefits in more complex lesions such as those with significant calcifications would still require further evaluation. Previous studies have highlighted a higher rate of ST related to the use of BRS [4, 32-34], but did not provide details on the effect of calcification. In our study, we see an observation pattern of higher early ST cases in the non-Ca group followed by a significantly higher rate of late ST in the Ca group. To the best of our knowledge, we believe the difference in timing on ST observed in the two groups is notable and interesting which warrant further studies. The observation of early ST in the non-Ca group (a group with a higher number of acute coronary syndromes; ACS) patients might be related to scaffold under sizing and to increased platelets activation. Predisposing factors of scaffold undersizing include the increased thrombus burden and vasoconstriction in the setting of acute STEMI leading to underestimation of the actual size of the infarct-related artery, thus increasing the

risk of the implantation of undersized scaffolds which can be seen even in the setting of metallic drug eluting stents [35]. Implantation of a relatively small scaffold in a relatively larger vessel can result in incomplete apposition, predisposing to ST [36]. Higher rates of ST were also previously noted in patients with ACS which could be due to reduction of early neointimal growth and strut coverage [37, 38]. Reasons for the increase in late ST in the Ca compared to the non Ca group include a role for technical factors such as suboptimal implantation with incomplete lesion coverage, underexpansion and malapposition [36, 39] and possibly greater impact on the scaffold endothelization and resorption process from a reduced MLD in the Ca group. The additional risks of late ST in the Ca lesions may arise from either the loss of radial strength after scaffold resorption (which typically commences 6 months to more than 1 year after scaffold implantation) or the scaffold 'dismantling' around calcified lesions which will have forces localized at the edge of the calcified areas where expansion tends to be asymmetrical [25]. Scaffold 'dismantling' might result in rapid changes in vessel wall architecture and therefore exert localized forces on the neo-intimal coverage potentially resulting in microdissections, triggering the thrombosis.

In our current study, though the event rate is similar between the Ca and non Ca groups, this may also be partially attributed to a higher ACS population in the non Ca group which is known to have higher risk of clinical events at follow up. In an earlier study evaluating the one-year outcomes in patients presenting with ACS compared to stable angina patients after implantation of a BRS from our centre, one-year clinical outcomes in ACS patients treated with BRS were similar to non-ACS patients. One-year definite ST rate was comparable: 2.0% for ACS population versus 2.1% for stable population (P=0.94), however, early ST occurred only in ACS patients [40]. Comparatively, overall ST rates were similar between the two groups in this study and further analysis did not show that Ca lesions were a significant predictor of ST (Table 2C). Of note, there was no difference in VLST between the Ca and non-Ca groups.

Though recent guidelines have supported a shift towards a shorter duration of DAPT [41], our findings on an increased late ST rate in Ca lesions may suggest that a longer duration of DAPT may still be necessary if BRS is to be implanted before the patient is to derive the potential benefits of BRS resorption. In our study, data on the use of dual antiplatelets therapy (DAPT) were available in the 395 patients whose follow up were available. All patients were prescribed aspirin during the duration of the study. Second generation $P2Y_{12}$ antiplatelet medications were used; clopidogrel (n=157, 39.7%), prasugrel (n=187, 47.3%) and ticagrelor (n=51, 12.9%). The median duration of DAPT was 365.00 (IQR 364.00 - 394.50) days and was similar between the 2 groups. In a study to evaluate the impact of DAPT termination on late and very late ST in patients treated with the Absorb BRS, the incidence of ST was low while on DAPT but potentially higher

when DAPT was terminated before 18 months [42, 43]. Further studies may be required to evaluate the effect of a prolonged duration of DAPT on the rate of late ST.

The findings showing a lesser acute lumen gain and similar 2 year MACE were consistent with previous research involving metallic DES in calcified versus non calcified lesions [8]. Moussa et al reported in a subanalysis of the TAXUS IV trial [8] a significant reduction in late lumen loss in calcific lesions (n=247) treated with PES vs. BMS (0.26±0.56 vs. 0.51±0.48 mm, p=0.015). In a study from the SPIRIT II trial by Onuma et al [44], the efficacy of EES in patients with at least one angiographically defined moderate calcific lesion (68 patients), was compared to those without any calcific lesion (144 patients). Late lumen loss was similar between the two groups at two years. No significant difference in two-year MACE rates was observed between the two groups (calcific vs. non-calcific: 10.9% vs. 4.4%, p=0.12). The numerically increased MACE rate was attributed to an increased ischaemia-driven TLR (7.8% vs. 1.5%, p=0.03). However TLR rates were similar between the Ca and non Ca groups in our study.

In summary, clinical outcomes of calcified and non-calcified lesions treated with BRS are in general similar except for late ST. Overall two-year MACE rates appear acceptable in patients with and without calcific lesions treated with BRS. Further larger randomized controlled trials comparing clinical outcomes of DES to BRS in calcified lesions may be required to evaluate the full impact of calcium on BRS outcomes compared to DES.

STUDY LIMITATIONS

This is a single-center, single-arm registry with no direct comparison with metallic DES. The total number of patients in this study was still limited. In addition, calcification assessment was based on angiographic classification alone rather than characterization of coronary calcification using alternative imaging modality such as intravascular ultrasound. Thus, these findings warrant further confirmation in a large-scale trial. Furthermore, deciding which patient or lesion was suitable for treatment with BRS could have resulted in selection bias. The event rate is unknown in the patients (n= 60, 13.2%) who did not agree to participate in further follow up and hence excluded from clinical outcome analysis. We further evaluated the population who did not agree to further follow up and compared the baseline demographic, lesion and procedural characteristics between the cases with calcified lesions and non- calcified lesions. There were significant differences in terms of age and use of predilation between the 2 groups which were similarly observed in the main population. Overall, the results are similar which provide support to our inference that the clinical outcomes reported in our study may be extrapolated to the patients whose clinical outcomes were not available. In addition, as our study was not powered to study clinical outcomes in relation to DAPT, we believe

that further studies may be required to evaluate if a prolonged duration of DAPT may reduce late onset ST in calcified lesions.

CONCLUSION

Careful more elaborate lesion preparation and the use of dedicated devices, such as scoring balloons and rotational atherectomy and intracoronary imaging were more likely encountered in Ca lesions. Even after more lesion preparation, acute gain and resulting final MLD by BRS implantation was less compared to non-calcified lesion. Clinical outcomes of calcified and non-calcified lesions treated with BRS were otherwise similar. However this is accomplished in the setting of appropriate case selection, adequate lesion preparation and scaffold optimization with attention to an adequate duration of dual antiplatelet in line with guideline recommendations. Interestingly, a different pattern of timing of ST was observed with no early ST but an increased late ST rate when implanted in calcified lesions.

Clinical Perspectives

Data on the impact of calcium (Ca) on outcomes in patients with lesions treated with bioresorbable vascular scaffolds (BRS) is limited, particularly in a "real world" study population. Careful more elaborate lesion preparation and the use of dedicated devices, such as scoring balloons and rotational atherectomy and intracoronary imaging were more likely encountered in Ca lesions. Late ST was more frequent in the Ca group compared to non-Ca group and no difference for VLST was observed. The findings merit further evaluation of clinical outcomes of BRS and the impact of implantation techniques in complex calcified lesions.

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Online Supplement

After exclusion criteria BVS STEMI and BVS Expand: 395 patients remain for analysis: 252 (63.8%) without calcification and 143 (36.2%) with a calcified lesion.

Univariate analysis (logistic regression) for calcification (yes/ no) to compute propensity score

Variables	OR (95% CI)	p value
Age	1.052 (1.030 – 1.075)	<0.001
Gender	1.125 (0.698 – 1.812)	0.630
DM	1.602 (0.923 – 2.781)	0.094
Dyslipidemia	1.552 (1.001 – 2.313)	0.050
Smoking	0.839 (0.721 – 0.977)	0.024
Presentation with ACS	0.465 (0.293 – 0.739)	0.001
HT	1.649 (1.086 – 2.504)	0.019
PAD	2.679 (1.116 – 6.434)	0.027
Previous MI	2.092 (1.139 – 3.842)	0.017
Multivessel disease	1.702 (1.108 – 2.615)	0.015
Small vessel	1.137 (0.721 – 1.792)	0.580
Bifurcation	2.253 (1.432 – 3.545)	<0.001
Total scaffold length per patient	1.029 (1.019 – 1.039)	<0.001
Average scaffold diameter per patient	0.701 (0.380 – 1.294)	0.256

Chapter 10

Mid-term CCTA results for Absorb bioresorbable vascular scaffold in clinical practice. A BVS Expand project

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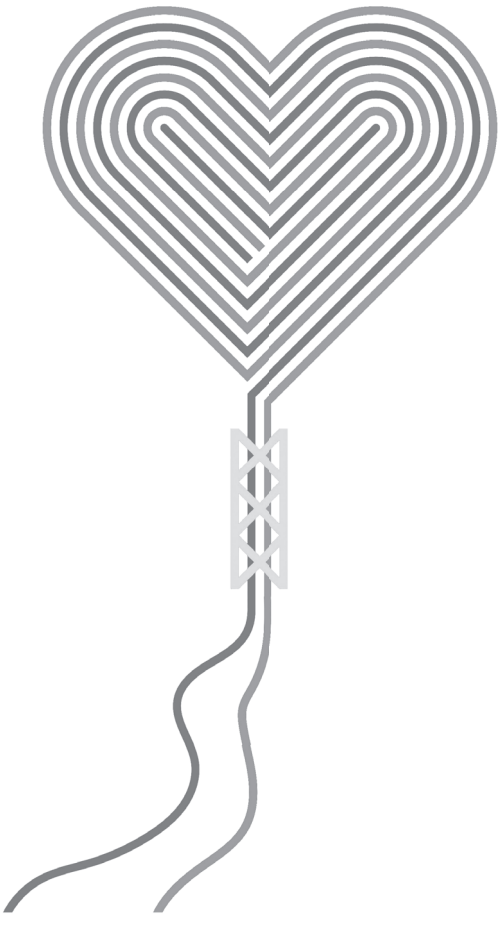

ABSTRACT

Objectives

To evaluate the mid-term coronary computed tomography angiography (CCTA) outcomes of the Absorb bioresorbable vascular scaffold (BVS) by non-invasive CT imaging in combination with CT perfusion.

Background

BVS were introduced with the aim of overcoming some of late events of metal drug-eluting stent (DES). Data regarding follow-up of BVS by use of CT is limited.

Methods

BVS-EXPAND, a single-centre study includes selected, real-world patients. Complex lesions such as bifurcation and long lesions were not excluded. Eighteen to 24 months after index procedure, consecutive suitable patients underwent CT. Main exclusion criteria were: contrast medium allergy, severe renal insufficiency, Target lesion revascularization (TLR) before CCTA. Additional CT perfusion was performed when a significant non-occlusive stenosis (> 50%) in the target lesion was identified on CCTA. CT-defined BVS success was defined as: stenosis< 50% on CCTA or CT perfusion without perfusion deficits.

Results:

The CCTA cohort consisted of 164 patients. CCTA's were assessable in 160 patients with 215 lesions and within that group, rate of BVS patency was 98.6% of the lesions. CT perfusion was necessary in 9 patients (lesions) with degree of stenosis > 50% and ruled out functionally significant restenosis in five. CT-defined BVS success was achieved in 207 lesions (96.7%); CT-derived failure occurred in 7 lesions (3.3%). Complete quantitative CCTA measures were available in 144 patients with in-scaffold minimal lumen area of 4.2 (± 1.7) mm^2, % area stenosis 10.3 ± 32.1%. Following CCTA three participants required revascularization.

Conclusions

CCTA was able to evaluate most BVS treated patients at mid-term follow-up, where additional perfusion imaging was a valuable addition, needed only in a small group of patients.

Condensed Abstract

This study investigated the CCTA outcomes to describe the mid-term performance of the Absorb BVS in more complex coronary lesions when examined by means of CCTA. Due to the invasiveness, costs of angiography and excellent performance of second-generation drug-eluting stents, routine follow-up after index PCI by invasive coronary angiography has disappeared from the spectrum. CCTA is a non-invasive method to investigate coronary lesions and CT perfusion is a valuable addition. CCTA was able to evaluate most BVS-treated patients at mid-term follow-up.

INTRODUCTION

Currently, percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is the gold standard for the treatment of coronary artery disease (CAD). In comparison with balloon angioplasty alone or PCI using bare metal stents (BMS), PCI with DES drastically decreased the rate of restenosis and revascularization. However on the long-term, DES with their permanent presence of foreign material are not devoid of drawbacks and have a stable average rate of reintervention of 2-4% after the first year. [1, 2] In an attempt to eliminate the potential (late) limitations of DES (neoatherosclerosis, very late stent thrombosis), bioresorbable scaffolds have been developed. The concept consists of a temporary device that restores the blood flow and temporally supports the vessel but that will fully resorb over time. The bioresorbable device most intensely investigated, is the ABSORB bioresorbable vascular scaffold (BVS. Abbott vascular, Santa Clara, CA, USA), which received both CE mark and FDA approval. It is a fully resorbable everolimus-eluting device made of a poly-L-lactide backbone with a poly-D, L-lactide coating. With the exception of two platinum markers at each end of the scaffold, this device is radiolucent and therefore does not interfere with non-invasive computed tomography of the coronary arteries. This is in contrast to metal stents, which cause blooming artefacts with subsequent hampering of luminal assessment. [3] Recently, mid-term outcomes RCTs that compared BVS with Xience, a second-generation everolimus eluting metal DES, showed that the BVS was associated with worse outcomes.[4] [5-7] These results were mainly driven by early scaffold thrombosis (ScT), triggered by the relatively thick struts of the first generation. Development of thin strut BVS is complex and expensive which first requires positive signals from long-term imaging and clinical follow-up.

Coronary computed tomography angiography (CCTA) could be such a technology and greatly improved over the last 20 years with an important increase in spatial and temporal resolution. The enhancement in CT technology enabled a reliable visualisation of the vessel lumen and also detection of significant coronary lesions.

A study by Collet and colleagues investigated the diagnostic accuracy of CCTA in ABSORB II and reported that accuracy regarding identification of presence and severity of obstructive CAD was similar between CCTA and coronary angiography at three years of follow-up. [8]

The aim of our study was to report mid-term CCTA outcomes to describe the mid-term performance of the Absorb BVS in more complex coronary lesions when examined by means of CCTA.

METHODS

Population

The BVS Expand registry is an investigator-initiated, prospective, single-centre, single-arm study performed in an experienced, tertiary PCI centre. In- and exclusion criteria have been described elsewhere. [9] In brief, patients presenting with NSTEMI, stable or unstable angina (UA), or silent ischemia caused by a *de novo* stenotic lesion in a native coronary artery treated with a BVS were included. Main exclusion criteria were patients with a history of coronary bypass grafting (CABG), presentation with ST-elevation myocardial infarction (STEMI) and patients with expected survival of less than one year. Complex lesions such as bifurcation, calcified (as assessed by angiography), long and thrombotic lesions were not excluded. As per hospital policy patients with a previously implanted metal DES in the intended target vessel were also excluded. Also, although old age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age.

For hospital quality control purposes of this new technique within the field of interventional cardiology, CCTA at mid-term follow-up (between 18 months and two years) was offered to all consecutive suitable patients. Exclusion criteria for undergoing a CCTA were contrast medium allergy, severe renal insufficiency, target lesion revascularization (TLR) performed before CCTA, severe calcification and patients who underwent cardiac imaging during the same time point.

Ethics

This is an observational study, performed according to the privacy policy of the Erasmus MC, and to the Erasmus MC regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the declaration of Helsinki. Approval of the ethical board of the Erasmus MC was obtained. All patients undergoing clinical follow-up provided written informed consent for the PCI and to be contacted regularly during the follow-up period of the study.

Procedure

PCI was performed according to current clinical practice standards. The radial or femoral routes were the principal routes of vascular access and 6 or 7 French catheters were used depending on the discretion of the operator. Pre-dilatation and post dilation were recommended with a balloon shorter than the planned study device length and with a non-compliant balloon without overexpanding the scaffold beyond its limits of expansion (0.5mm > nominal diameter) respectively. Intravascular imaging with the use of Intravascular Ultrasound (IVUS) or Optical Coherence Tomography (OCT) was used for

pre-procedural sizing and optimization of stent deployment on the discretion of the operator.

Angiographic analysis

Baseline quantitative Coronary Analysis (QCA) was performed by a total of three different independent investigators. Coronary angiograms were analysed with the CAAS 5.10 QCA software (Pie Medical BV, Maastricht, the Netherlands). The QCA measurements provided reference vessel diameter (RVD), percentage diameter stenosis and minimal lumen diameter (MLD).

CCTA

Second and third-generation dual source CT scanners (SOMATOM Definition Flash and SOMATOM Force, Siemens Medical Solutions, Forchheim, Germany) were used. Standard acquisition techniques for coronary techniques were used: Sublingual nitroglycerin was given to all patients. Beta-blockers were optional in patients with a fast heart rate.

A prospective electrocardiographically triggered axial scan mode was used, with an exposure window during diastole and/or systole depending on the heart rate. Tube current and tube voltage were selected semi-automatically on the basis of body size. For CCTA imaging, a contrast bolus of approximately 50 to 60 ml (depending on iodine concentration and expected scan duration) was injected, followed by a saline bolus chaser. Images were reconstructed with a medium smooth kernel (B26, Bv40) and a slice thickness of 0.5-0.7 mm at 5% intervals of the acquired R-R segment. [10]

Scaffold patency was described as a scaffolded tract with a visible lumen and the possibility to evaluate contrast attenuation. First and according to normal practice, the CCTA was evaluated by a radiologist. Lesions were then divided into three groups: no abnormalities identified in target lesion, abnormalities seen but non-significant, significant stenosis (suspected) or total occlusion.

CT perfusion

Experienced CT readers (KN or RB) evaluated the CT angiograms, using PCI procedural information on BVS sizes and location but blinded to all other modalities. They set indication for any additional CT myocardial perfusion scans in case of a significant, non-occlusive stenosis on CCTA. This CT myocardial perfusion scan was performed in a separate session.

The dynamic CT myocardial perfusion scan was performed to further determine the functional significance of a morphological significant stenosis detected on CCTA. In a dynamic CT myocardial perfusion scan a series of acquisitions is made during the first pass of a contrast bolus, while the patient is in a hyperaemic state. After 3 min of adenosine infusion (at 140 µg/kg/min) the dynamic CT myocardial perfusion scan was started.

Fifty ml of contrast medium (Ultravist, 370 mgI/ml; Bayer, Berlin, Germany) was injected at 6 ml/s, followed by a saline bolus of 40 ml. A shuttle mode was used to cover the left ventricle acquiring images in alternating cranial and caudal table positions. CT dynamic myocardial perfusion acquisition was started 5 seconds after the start of the contrast medium injection and patients were asked to hold their breath during the entire acquisition (30-35 seconds) [10, 11]. The change in attenuation of the myocardium due to the first pass of the contrast bolus was used to compute myocardial blood flow maps using a hybrid deconvolution model. A functionally significant coronary (re)stenosis would result in a reduction of the myocardial blood flow in the associated myocardial territory [12]. By visual inspection, the myocardial blood flow maps in combination with the CTA potential ischemia causing (re)stenosis of the BVS were identified by an expert CCTA reader (KN).

Quantitative CCTA analysis

In a subgroup of patients, quantitative data of the lesion of interest were analysed off-line by a radiologist on a dedicated workstation using commercially available software Syngo. Via (Siemens, Forchheim, Germany) to perform a quantitative CTA analysis. The optimal imaging phase and the centre lumen line through the treated vessel was automatically selected by the software and manually adjusted when needed. Cross-sections of the vessel were reconstructed, extending approximately 5 mm beyond the device (proximal and distal segments), using the platinum scaffold markers as landmarks. Every BVS was evaluated at three locations: 1. the proximal scaffold segment (defined as the segment extending from the platinum marker to five mm proximal to the marker, was evaluated first by using Syngo.Via to detect the minimal lumen and to determine the lumen areas. An automatic tracer was used and in case of insufficient contrast lumen opacification, it was manually adjusted; 2. the distal scaffold segment (defined as the segment extending from the platinum marker to five mm distal to the marker), was evaluated in the same fashion; 3. the minimal scaffold lumen was assessed by visually selecting the minimal lumen area inside the scaffold (Figure 1). At each location the cross-sectional lumen area surface was measured. If multiple overlapping scaffolds were inserted, they were considered as one lesion; if none were overlapping, they were considered as separate. Reference vessel area was calculated as the average of the proximal and distal lumen reference area segments. The lumen area stenosis was calculated as follows: reference lumen area minus the minimal lumen area as a percentage of reference lumen area. In case of a bifurcation lesion with a large side branch elucidating a significant step down, the reference lumen diameter was based on measures of the distal end only.

Quantitative CTA analysis could not (completely) be performed in case of poor image quality (motion artefacts, insufficient contrast lumen opacification), ostial lesion, too small vessel calibre and total occlusion.

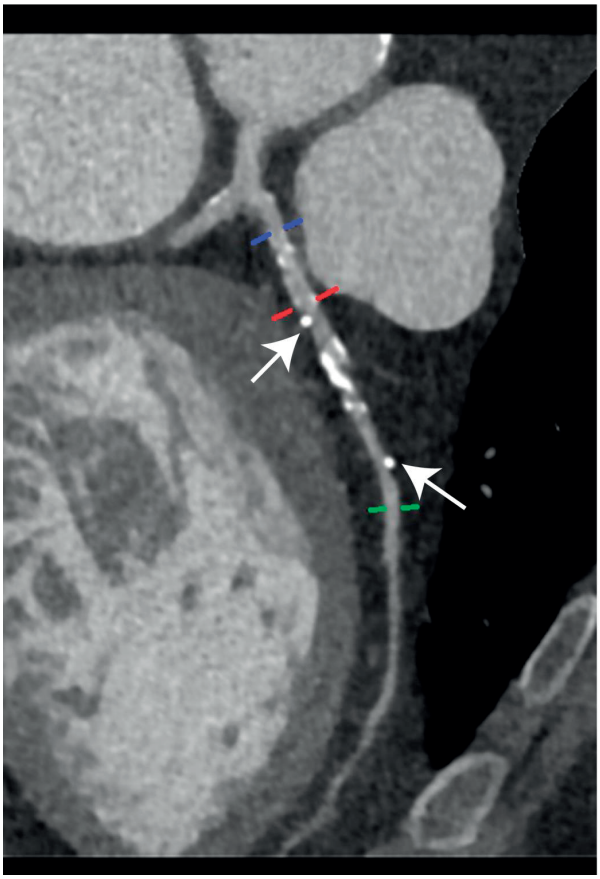

Figure 1 Example QCT measurement
Example of a normal QCT measurement: the blue line shows the proximal reference (5-10 mm distance from proximal scaffold edge), the red line indicates the proximal scaffold border (0.3mm distance from proximal scaffold edge). The green line is the distal reference (5-10 mm distance from distal scaffold edge). The white arrows indicate the two pairs of platinum scaffold markers.

Follow-up

Follow-up information specific for hospitalization and cardiovascular events was obtained through questionnaires or telephone interviews at multiple time points (1 month, 6 months, 1, 2, 3 and in the end: 4 and 5 years). If needed, medical records or discharge letters from other hospitals were requested. Events were adjudicated by an independent clinical events committee (CEC). All information concerning baseline characteristics and follow-up was gathered in a clinical data management system.

Definitions

CCTA feasibility was the percentage of patients with sufficient image quality to assess the target lesion on CCTA. BVS patency was defined as an open vessel at the site of BVS implantation. CT-defined BVS success was described as no stenosis of target lesion, diameter stenosis of < 50% on CCTA or (possible) stenosis of ≥ 50% but with a normal additional myocardial perfusion scan. CT-defined BVS failure was defined as stenosis ≥ 50% on CCTA combined with perfusion deficits during perfusion CT or complete occlusion on CCTA. Definitions of events were as in our previous publication. [9]

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation. Quantitative CCTA measures are described as median with interquartile range (IQR). The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical tests were two-sided and the P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 21 (IL, US).

RESULTS

After applying the exclusion criteria, 195 consecutive patients were invited as suitable for follow-up CCTA, of which 164 accepted the offer. In four patients, poor CCTA quality made any image assessment impossible and thus 160 patients with 215 lesions remained for analysis (Figure 2). In one lesion, patency was assessable but detailed information of degree of stenosis could not be provided.

Figure 3 is an example of a patient with two sequential lesions in the RCA treated with two 28 mm long overlapping BVS with excellent acute outcome. Follow-up CCTA identified an excellent result, even at the location of the overlap.

Baseline characteristics

Table 1 summarizes baseline characteristics of patients, lesions and certain procedural factors of the whole CCTA cohort (n=160). Mean age was 59.9 ±10.0 years, 76.3% were male, 11.9% diabetics and 60.0 % presented with ACS.

The LAD was the coronary artery most frequently treated (53.2%). AHA/ ACC lesion type B2/ C was present in 37.2%, bifurcation in 22.5%, calcification (moderate or severe on angiography) in 39.0%. Pre-dilatation was performed in 89.4%, with a balloon to artery ratio of 1.07. Intravascular imaging using OCT or IVUS was carried out in 58%. Post-dilatation was performed in 51.8% with a maximum post-dilatation balloon inflation

pressure of 15.5 (±3.24) atm. Post-procedural MLD was 2.3 (±0.4) mm, post-procedural % diameter stenosis was 16.5 (±9.3) %.

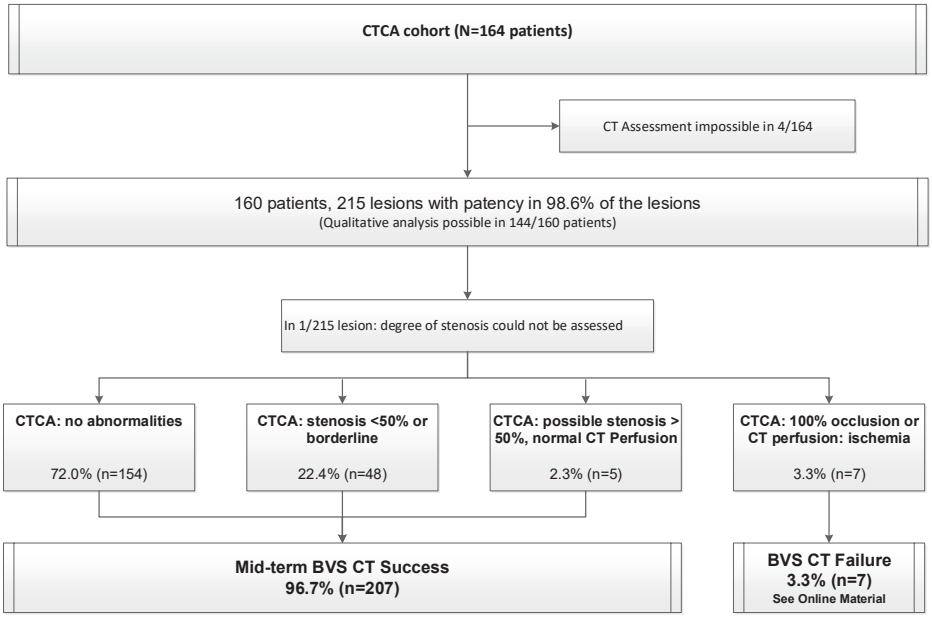

Figure 2 Flowchart of the study

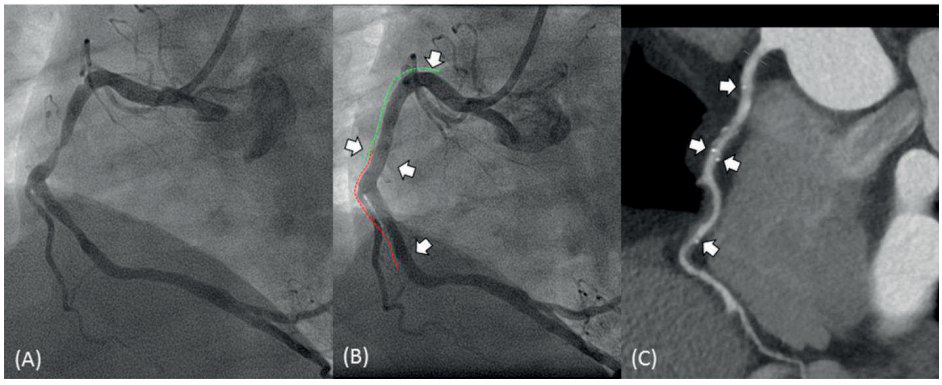

Figure 3 Case description 1

Figure 3 is an example of a successful case. It concerns a 40-year old male, smoking patient with diabetes, dyslipidaemia and a positive family history for CAD. He presented with NSTEMI due to two-vessel disease of the RCA (A) and LAD. The RCA was treated with pre-dilatation, BVS (2x 3.5*28) and post-dilatation (B) The LAD showed a positive FFR (0.75) and one 2.5*18mm BVS was implanted, followed by post-dilatation. He underwent his CCTA 861 days after baseline PCI and all BVS were patent without signs of stenosis (See C for CCTA result of RCA during follow-up).

Table 1. Baseline characteristics

Patient (n=160)	
Age (mean ± SD), years	59.86 (±10.0)
Male gender, %	76.3
Diabetes mellitus, %	11.9
Current smoker, %	33.8
Dyslipidaemia, %	51.9
Hypertension, %	55.0
Family history of CAD, %	46.9
Prior myocardial infarction, %	17.5
Prior PCI, %	10.6
Presentation with ACS, %	60.0
Lesion (n= 215 lesions)	
Treated vessel , %	
LAD	53.2
LCX	22.5
RCA	24.3
AHA/ ACC lesion classification type B2 /C, %	37.2
Calcification	39.0
Bifurcation	22.5
CTO	4.1
Procedure	
Pre-dilatation (%)	89.4
Max pre-dilation balloon diameter (mean ± SD), mm	2.62 (±0.39)
Pre-dilation balloon: artery ratio	1.07 (±0.23)
Post-dilatation (%)	51.8
Maximum post-dilatation inflation pressure (mean ± SD), atm	15.50 (±3.24)
Intravascular imaging (%)	58.1
Pre-procedural RVD (mean ± SD), mm	2.54 (±0.47)
Post-procedural MLD (mean ± SD), mm	2.30 (±0.40)
Post-procedural diameter stenosis, %	16.54 (±9.25)
Lesion length (mean ± SD), mm	23.97 (±13.10)

CAD: coronary artery disease, CTO: chronic total occlusion, MLD: minimum lumen diameter, PCI: percutaneous coronary intervention, RVD: reference vessel diameter. Values are mean (±SD) or median (interquartile range)

CCTA

Median duration from index procedure until CCTA was 714 (IQR: 639 – 754) days. See Table 2 for median dose length product (DLP) and effective dose.

When assessed by CCTA, in 98.6 % of the 215 lesions BVS patency was achieved. In one lesion, degree of stenosis could not be assessed.

Table 2. CCTA (perfusion) acquisition

CCTA (n= 160)	
CTDIvol (mGy)	19.52 (13.36 – 35.17)
DLP (mGy-cm)	288.15 (186.15 – 473.55)
Radiation effective dose (mSv)	4.09 (2.63 – 6.73)
CT perfusion (n = 9)	
CTDIvol (mGy)	37.24 (25.00 – 45.06)
DLP (mGy-cm)	338.10 (238.93 – 441.83)
Radiation effective dose (mSv)	5.51 (3.70 – 6.44)
Tube voltage (KV)	70 (70 – 70)

CCTA: Computed tomography coronary angiography, CTDI: CT dose index, DLP: dose length product. Values expressed as median (interquartile range)

In 154/ 214 lesions (72%) no target lesion abnormalities were seen on CCTA. In 53 lesions (24.7%) some non-significant changes, representing minor neo-intima hyperplasia, were seen. In 12 lesions (5.6%, 12 patients) an anatomical significant stenosis of the target lesion was reported. Three of them showed total occlusion.

CT Perfusion

In four patients, BVS failure was identified by additional CT perfusion. Figure 4 demonstrates an example of a patient with two BVS (2.5*28mm) in the LAD for spontaneous coronary artery dissection. CCTA showed ISR at level of the second scaffold and the additional CT perfusion revealed a small area of ischemia. Therefore, CT-defined BVS success was 96.7% of the lesions (Figure 2).

Two patients were subsequently treated by PCI. The other patients were initially treated conservatively, of whom one was treated through PCI during follow-up (> two years post-CCTA). However, during this re-intervention, only a non-target vessel was treated. FFR of the target-vessel was negative and the BVS was patent. In patients who did not have anatomically or functionally significant stenosis, no events occurred during follow-up.

Quantitative CCTA

Complete quantitative analysis was available in a subgroup of 144/160 patients with 194 lesions (Table 3). Quantitative analysis of the lesion was not possible in case of the presence of total occlusion (n= 3 patients), vessel calibre of too small diameter (n=3), too much calcification (n=3), insufficient amount of contrast (n=4) or motion artefacts (n=8).

In-scaffold minimal lumen area was 4.2 ± 1.7 mm^2. In-scaffold percentage area stenosis was 10.3 ± 32.1. In-segment area stenosis was 30.6 ± 25.2 %. Lesions that showed significant abnormalities on CCTA had smaller but non-significant reference areas: 4.3 vs 5.8 mm^2, p=0.69. Out of the seven patients with CT-defined BVS failure, five had MLD <

2.4 mm at baseline. Patients with a suboptimal result post-PCI (MLD <2.4 mm), showed smaller MLA during follow-up CT: 3.9 vs 4.7 mm^2 (p=0.03).

Table 3. Quantitative CCTA Assessment

	Total
In-scaffold, mm^2	
Minimal lumen area (mean ± SD)	4.2 ± 1.7
Median reference area (mean ± SD)	5.0 ± 2.1
Area stenosis, % (mean ± SD)	10.3 ± 32.1
In-segment, mm^2	
Area stenosis, % (mean ± SD)	30.6 ± 25.2

Values described as mean ± standard deviation (SD) or median (interquartile range [IQR])

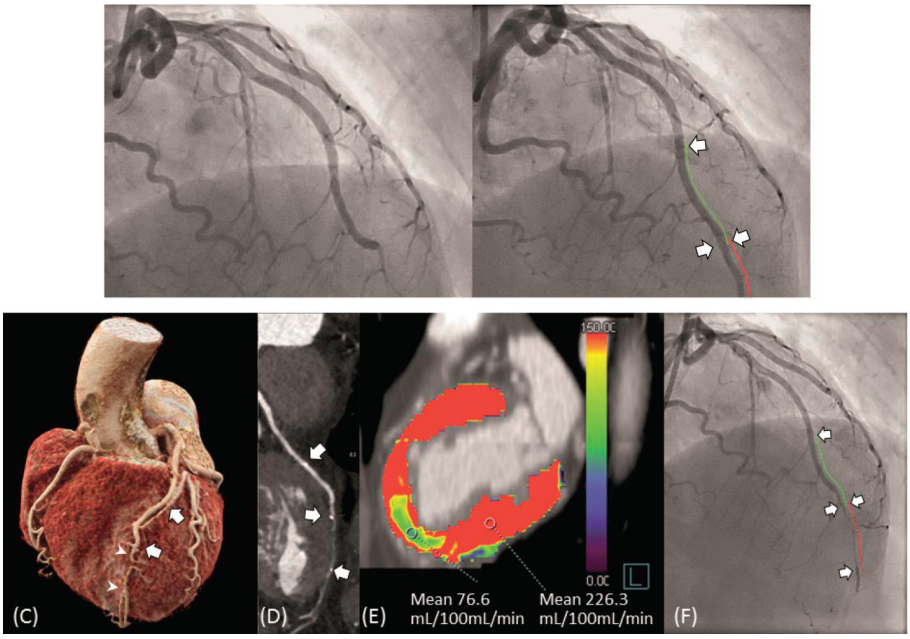

Figure 4 Case description 2
A 53-year old female patient presented with an anterior STEMI based on an intramural haematoma. (A) For TIMI I flow, initial balloon angioplasty did not result in stable TIMI III flow due to acute recoil for which two overlapping 2.5 x 28 mm BVS scaffolds were implanted (B). Follow-up CTCA (C and D for 3D image) showed a well patent proximal scaffold with minimal contrast in the distal scaffold suggestive for scaffold failure. CT-perfusion (E) demonstrated localised ischemia in the territory of the distal LAD. Subsequent angiography (F) confirmed target lesion failure, mainly due to late recoil and minimal neo-intima on IVUS which was successfully treated with balloon angioplasty only. Subsequent follow-up for one year was without recurrent events.

Clinical outcomes

Clinical outcomes (reported as Kaplan-Meier estimates) are described in Table 4. Median duration of follow-up after baseline PCI was 1456.50 (IQR: 1098.25 – 1472.50) days and follow-up of at least three years post-PCI was available in 85.6%. We focussed on events that took place after CCTA and up to three years after baseline PCI. Those event rates were as follows: rate of death was 0.7% (one patient, non-cardiac cause); rate of MI was 0% and TLR rate was 3.5%. There were no cases of scaffold thrombosis. In three patients, TLR occurred after CCTA

Table 4. Clinical outcomes, described as Kaplan-Meier estimates (n =160 patients)

	Post-CCTA
Death, % (n)	0.7 (1)
Cardiac death, % (n)	0.0 (0)
Myocardial infarction, % (n)	0.0 (0)
Target lesion revascularization % (n)	3.5 (3)
Target vessel revascularization, % (n)	3.5 (3)
Non-target vessel revascularization, % (n)	2.8 (4)
Definite/ probable scaffold thrombosis, % (n)	0.0 (0)

DISCUSSION

In this sub-cohort of the BVS Expand registry, we have reported on the mid-term CCTA and clinical outcomes of a sub-cohort of patients treated with the ABSORB BVS for a variety of lesion complexity. The main findings were as follows: 1) CCTA was a successful tool to establish non-invasively CT-derived BVS success at mid-term follow-up in almost all patients including more complex lesions. 2). Additional CT perfusion imaging provides important functional information in moderate or severe restenotic lesions. 3) Non-clinical CT-derived BVS failure is a rare event. 4) Patients with CT-derived BVS success at mid-term were free from thrombosis or TLR during follow-up after CT imaging.

Our study demonstrated that even in patients with more complex anatomy, CCTA could be routinely used to follow-up the patients after BRS implantation. Patency was 98.6% and the rate of adverse events after CT, was low. When compared to the ABSORB Cohort A and B studies in which CCTA was also performed [13, 14], the percentage of calcification, longer lesion length and AHA/ ACC lesion classification type B2/C illustrates the higher complexity of our patient population. Polymeric BRS technology, through its radiolucency and complete resorption, could be very suitable for non-invasive follow-up. Evaluation of newly introduced technologies in medicine after initial approval is essential. Patients in routine practice differ importantly from patients studied in approval studies where success rates reported in first-in-man studies and RCT including highly

selected patients, are generally higher. Most post-approval investigator-initiated studies rely only on clinical follow-up specific protocols and, in the best case, independent event adjudication by experienced investigators. Invasive coronary angiography has been the objective standard to establish metallic stent patency and presence of in-stent restenosis. Due to the invasiveness, costs of angiography and excellent performance of second-generation DES, routine follow-up after index PCI by invasive coronary angiography (ICA) has disappeared from the spectrum. CCTA is a non-invasive image modality with a high sensitivity and relatively low specificity, particularly for identification of hemodynamically significant CAD. Evaluation of BVS using CCTA was described in several publications and appeared to have a high diagnostic accuracy. [8, 13, 15] [16] Our study lacked validation with angiography; however, a recent study concluded that the accuracy of the Absorb BVS to detect in-scaffold luminal obstruction, when angiography and IVUS were used as references, was high. [17]

Investigation of efficacy after local introduction of new technology with the best feasible techniques should be routine for every hospital. [18]

In our cohort, in only four patients image quality was not sufficient to assess scaffold patency, let alone severity of stenosis or even quantitative CT measures. Rate of patency and also mid-term CT-defined BVS success were high. Our study showed that when a CT perfusion was performed, perfusion deficits were seen in approximately 50% of the cases. The advantage of CT perfusion is the possibility to perform it on-site and in the same session as CCTA. CT perfusion improves the performance of CCTA in the identification of functionally significant CAD and also improves specificity. [10, 19]

In order to discriminate between lesions that are hemodynamically significant and those who are not and with the aim of diminishing unnecessary referrals for ICA, physiological assessment of the target lesion is of importance. One of the possibilities is by using quantitative vessel analysis [20] or MR perfusion[21] and CT-derived fractional flow reserve (FFR_{CT}).[10, 19] Quantitative CTA analysis improved specificity from 41% - 76% for percentage area stenosis [22] and accuracy from 49% - 71% for percentage diameter stenosis. [20]

FFR_{CT} has been advocated as additional technology to improve specificity of CCTA, revealing good diagnostic accuracy. [23] Several studies have investigated FFR_{CT}. [19, 24-27] Currently, the HeartFlow FFR_{CT} is the only the FDA-approved CCTA derived FFR platform, which can be used off-site only and at significant costs. As so, we selected CT perfusion for our research.

Post-CCTA adverse events up to three years after baseline PCI occurred in only three patients. In all of the other patients, no adverse events of the target lesion were reported after CCTA was performed and therefore this appeared as a rare event. In comparison to other mid-term clinical results [28], outcomes at three years are good with a low rate of death and no cases of ScT.

Findings of our study show that CCTA is feasible in patients treated with Absorb BVS, which can be useful information also for other bioresorbable devices, as the current generation BVS has been taken out of the market.

CONCLUSION

CCTA was able to evaluate most BVS-treated patients at mid-term follow-up. Rates of patency and CT-defined BVS success were high. Additional perfusion imaging was a valuable addition, needed only in a small group of patients. Clinical outcomes at three years were promising without cases of scaffold thrombosis and no TLR post-CT when CCTA results were good.

LIMITATIONS

The size of our CCTA cohort was relatively limited. There might have been selection bias at the moment patients were included in the CCTA cohort. Quantitative assessment was not possible in all of the patients. Variations in image quality occurred due to calcification and platinum markers causing blooming, motion artefacts. Lastly, there was no validation with angiography or intravascular imaging.

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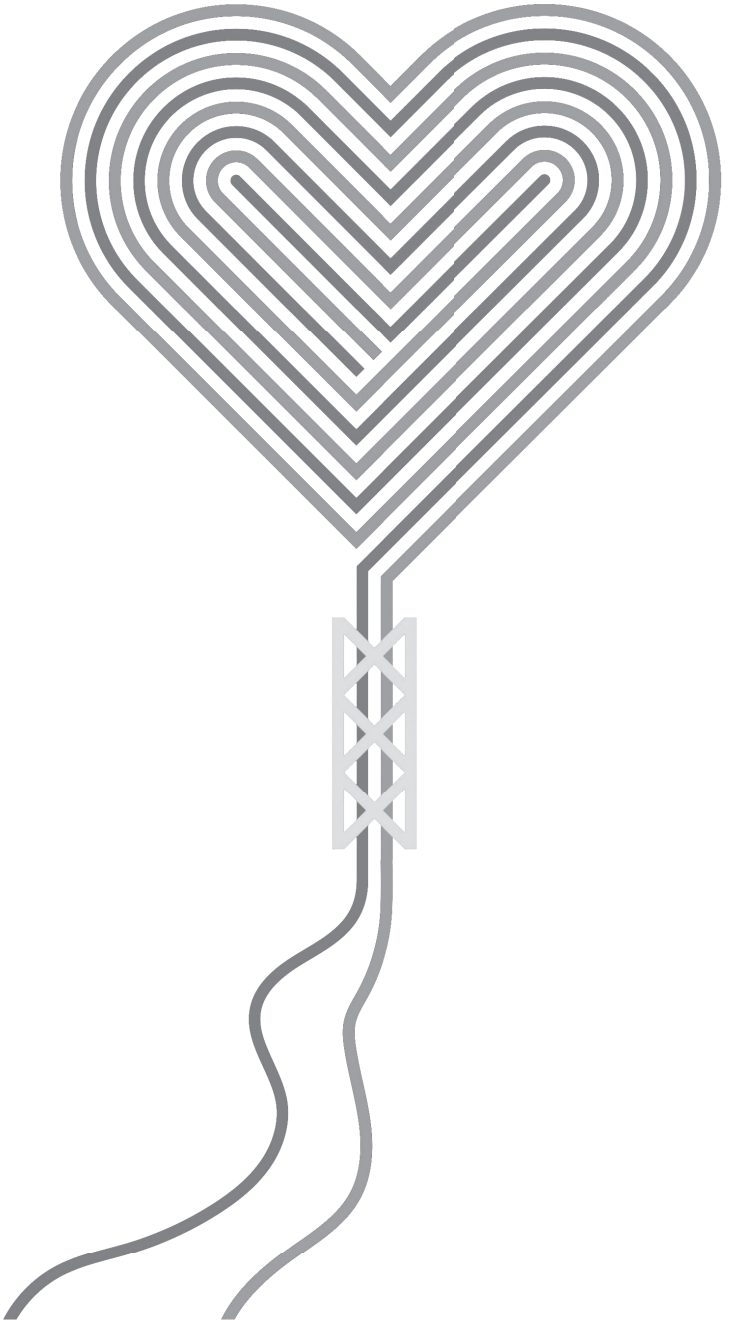

Part III

Implications of failed cases for future applications

Chapter 11

Angiographic and optical coherence tomography insights into bioresorbable scaffold thrombosis: single-centre experience

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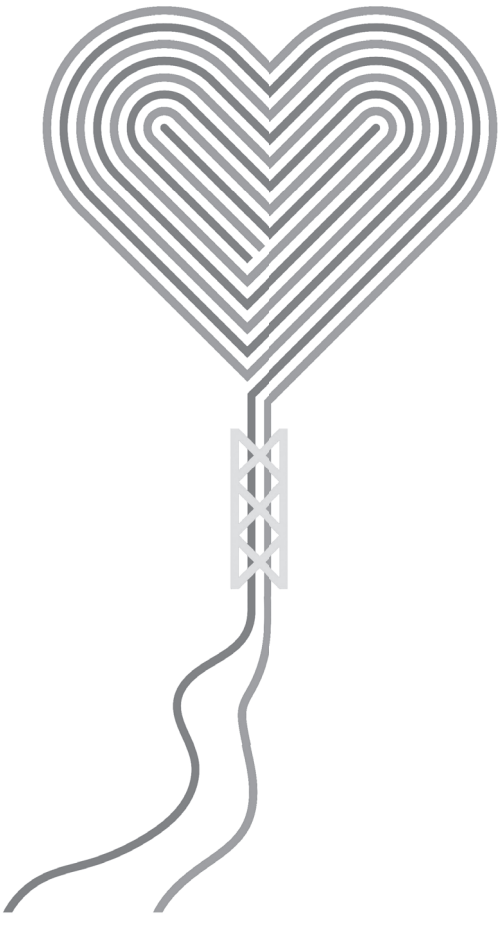

ABSTRACT

Background

As bioresorbable vascular scaffolds (BVSs) are being increasingly used in complex real-world lesions and populations, BVS thrombosis cases have been reported. We present angiographic and optical coherence tomography (OCT) findings in a series of patients treated in our center for definite bioresorbable scaffold thrombosis.

Methods and Results

Up to June 2014, 14 patients presented with definite BVS thrombosis in our centre. OCT was performed in 9 patients at the operator's discretion. Angiographic and OCT findings were compared with a control group comprising 15 patients with definite metallic stent thrombosis. In the BVS group, time interval from index procedure to scaffold thrombosis ranged from 0 to 675 days. Incomplete lesion coverage by angiography was identified in 4 of 14 cases, malapposition by OCT in 5 of 9 cases, strut discontinuity in 2 of 9 cases, and underexpansion in 2 of 9 cases. Five patients had discontinued dual antiplatelet therapy, and in 3 of them discontinued dual antiplatelet therapy discontinuation had occurred the week preceding the event. There were no significant differences in angiographic or OCT findings between BVS and metallic stent thrombosis.

Conclusions

Suboptimal implantation with incomplete lesion coverage, underexpansion, and malapposition comprises the main pathomechanism for both early and late BVS thrombosis, similar to metallic stent thrombosis. Dual antiplatelet therapy discontinuation seems to also be a secondary contributor in several late events. Our observations suggest that several potential triggers for BVS thrombosis could be avoided.

INTRODUCTION

Metallic drug-eluting stents (DESs) are the current standard for invasive treatment of coronary artery disease. However, metallic DES have been associated with late complications such as neoatherosclerosis and incomplete healing that can lead to failure even at long-term follow-up.1–3 Bioresorbable vascular scaffolds (BVSs) are a new treatment for coronary artery disease that could potentially alleviate such problems.4,5 To date, bioresorbable scaffolds have been evaluated in first-in-man or highly selected study cohorts with simple lesions in low-risk patient populations,4–7 whereas vascular response in lesions of real-world patients might differ. As BVSs are being increasingly used in more complex lesions, several cases of BVS thrombosis have been reported.8–10

In metallic DES, intravascular imaging has elucidated pathophysiologic mechanisms of stent thrombosis, underscoring the significance of procedural factors such as inadequate stent expansion and vascular trauma for acute thrombosis11, 12 or delayed healing and neoatherosclerosis for late thrombosis.1, 2 Whether BVS thrombosis is amenable to the same factors remains unknown.

We aimed to present angiographic and optical coherence tomography (OCT) findings in a series of patients with definite bioresorbable scaffold thrombosis treated in our catheterization laboratory and compare them with a control group of patients with definite metallic stent thrombosis.

METHODS

Study Population

The everolimus-eluting BVS (Absorb; Abbott Vascular, Santa Clara, CA) has been used in clinical trials in our centre since 2006.4–7 Since September 2012, Absorb BVS was approved for commercial use in the Netherlands and has been used in our centre also in more complex patients and lesions, while outcomes of these patients are recorded in the Expanded Clinical Use of Everolimus Eluting Bioresorbable Vascular Scaffolds for Treatment of Coronary Artery Disease (BVS- Expand) and Everolimus-Eluting Bioresorbable Vascular Scaffolds for Treatment of Patients Presenting With ST-Segment–Elevation Myocardial Infarction (BVS-STEMI) registries.13, 14 Up to June 1, 2014, a total of 733 everolimus-eluting BVS had been implanted in 469 patients in our centre.

Since 2006 and up to June 2014, 14 patients were admitted to our laboratory because of definite BVS thrombosis. Definite BVS thrombosis was identified using the Academic Research Consortium definition requiring both angiographic evidence of scaffold thrombosis (including 5-mm edge segments) and clinical evidence of acute coronary syndrome and were classified as acute, subacute, late, or very late.15 Treatment of BVS

thrombosis, including thrombus aspiration or invasive imaging, was performed at the operator's discretion. All patients have provided informed consent.

To understand potential differences and similarities between BVS and metallic stent thrombosis, we used consecutive patients with definite metallic stent thrombosis as control. Between September 1, 2012 and June 1, 2014, 55 patients presented with definite metallic stent thrombosis. We excluded patients with stent thrombosis in left main or in graft (n=4), as these typically large vessels are not suited for BVS with its currently limited diameter range, and patients with very late stent thrombosis >2 years since implantation (n=36), as the available follow-up period in BVS does not allow a meaningful comparison of very late thrombosis at that interval. Thus, 15 patients with definite metallic stent thrombosis were included as control (2 acute, 4 subacute, 5 late, and 4 very late between 1 and 2 years).

Angiographic Analysis

Angiographic analysis was performed for baseline implantation and for stent/scaffold thrombosis, including quantitative coronary angiography and assessment of intra-procedural complications. Incomplete lesion coverage (also called geographical miss) was defined as the longitudinal mismatch between implantation site and diseased coronary segment or coronary segment subjected to balloon dilatation, and its identification required a consensus characterization by 2 observers that reviewed the baseline angiography, applying established methodology.16 Angiographic analysis at the event included assessment of thrombolysis in myocardial infarction flow grade, thrombus burden,17 and quantitative coronary angiography measurements.

OCT Image Acquisition

OCT was performed at the operator's discretion, after thrombus aspiration, in 9 patients with BVS thrombosis and in 5 patients with metallic stent thrombosis. OCT acquisition was performed with the Lightlab/St Jude (C7XR/Illumien, St Jude/Lightlab, St Paul, MN) or the Terumo Lunawave (Terumo Corporation, Tokyo, Japan) frequency-domain imaging systems, as previously described.4, 14

OCT Image Analysis

OCT image analysis was performed offline in 1-mm intervals within the treated segment, including proximal and distal 5-mm long edge segments, after excluding frames with <75% lumen contour visibility, as previously described.1,7,14 Scaffold struts were defined malapposed in the absence of contact with the vessel wall, whereas metallic stent struts were malapposed when the distance of the adluminal strut reflection from the vessel wall exceeded the nominal strut thickness (metal backbone plus coating). These definitions do not include struts in front of side-branches or their ostium (polygon of

confluence), which are defined as side- branch–related struts. Intraluminal struts belonging to adjacent clusters of apposed struts in overlapping scaffolds were not considered malapposed. Thrombus was defined as irregular endoluminal or mural mass and scaffold discontinuity (in BVS) as struts overhanging each other at the same angular sector, with or without malapposition, or isolated struts at the luminal centre without obvious connection to other surrounding struts,7,18 further classified as fracture (present at baseline and follow-up) or late discontinuity (present only at follow-up). OCT findings in BVS thrombosis were compared between frames with and without thrombus.

Statistical Analysis

All analyses were performed with SPSS 20.0 (IBM, Chicago, IL). Continuous variables are presented as mean ± SD, median [inter- quartile range], or estimated means (95% confidence interval), whereas categorical variables are reported as count and percentages. Differences in continuous baseline or angiographic variables were assessed with *t* test, whereas in categorical variables with the $\chi 2$ or Fisher exact test. Differences in OCT variables were assessed with Mann–Whitney and paired comparisons with Wilcoxon, because of the small sample size and skewed nature of these variables. Frame- or strut-level analysis was performed with mixed linear or logistic regression, as struts are clustered within each frame within each patient. Strut-level malapposition was assessed by mixed logistic regression using within-frame and within-patient intercepts as random effects. Frame-level differences were assessed with mixed linear or logistic regression analysis using within-patient intercepts as random effect. All *P* values are 2-sided with a value <0.05 indicating significance.

RESULTS

Baseline Characteristics and Concomitant Therapy Baseline characteristics for BVS (n=14) and metallic stents (n=15) are reported in Table 1. There were no significant differences in baseline characteristics with the exception of a higher proportion of men in BVS (100% versus 67%; *P*=0.042).

At the time of BVS thrombosis, 5 patients were not receiving dual antiplatelet therapy (DAPT) (2 with premature dis- continuation <1 year and 3 with planned discontinuation >1 year). In three patients, DAPT discontinuation had occurred the week preceding the event. In metallic stents, complete DAPT discontinuation <1 year was confirmed in 1 patient and BVS compared with metallic stents (predilation: 92.9% versus 50.0%; *P*=0.033 and post-dilation: 50.0% versus 0%; *P*=0.006), with a trend for higher scaffold diameter in (3.18±0.27 versus 2.90±0.47; *P*=0.06). OCT post implantation had been performed in 5 of 14 patients in BVS and in none of the metallic stents. Incomplete lesion coverage was

observed in four BVS cases, and in one case with metallic stent. Two patients with BVS had an angiographically visible edge dissection (one proximal, one distal) after baseline implantation, left untreated.

Table 1. Clinical and demographic characteristics

	n=14
Age (years)	60.2±10.5
Male n(%)	14(100)
Clinical syndrome at baseline	
Stable angina n(%)	5(35.7)
Unstable angina n(%)	1(7.1)
NSTEMI n(%)	3(21.4)
STEMI n(%)	5(35.7)
Clinical syndrome at scaffold thrombosis	
NSTEMI n(%)	7(50.0)
STEMI n(%)	7(50.0)
Antiplatelet therapy at scaffold thrombosis	
Aspirin n(%)	11(78.6)
Clopidogrel n(%)	3(21.4)
Prasugrel n(%)	5(35.7)
Ticagrelor n(%)	1(7.1)
Oral anticoagulation n(%)	3(21.4)
CAD risk factors	
Hypertension n(%)	9(64.3)
Dyslipidemia n(%)	6(42.9)
Diabetes n(%)	1(7.1)
Smoking n(%)	6(42.9)
Family history of CAD n(%)	5(35.7)
Comorbidities	
Prior cerebrovascular accident n(%)	3(21.4)
Peripheral vascular disease n(%)	1(7.1)
Kidney disease n(%)	0(0.0)
Prior MI n(%)	2(14.3)
Prior PCI n(%)	2(14.3)
Prior CABG n(%)	0(0.0)
COPD n(%)	1(7.1)

Abbreviations: NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; CAD=coronary artery disease; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease

OCT Findings

OCT at thrombosis was performed in 9 of 14 patients with BVS and in 5 of 15 patients with metallic stents. There was no significant difference in OCT findings between BVS and metallic stent thrombosis (Table 4). In (very) late thrombosis, the incidence of malapposed struts was 1.9%±2.2% for BVS versus 5.6%±6.2% for metallic stents (*P*=0.31), and malapposition distance 486±225 µm for BVS versus 265±151 µm for metallic stents (*P*=0.17).

In BVS thrombosis, frames with thrombus had lower lumen (4.35 mm2 [2.61–6.08 mm2] versus 5.84 mm2 [4.11–7.58 mm2]; *P*<0.001) and scaffold area (7.63 mm2 [6.32–8.95 mm2] versus 8.14 mm2 [6.83–9.46 mm2]; *P*<0.001) com- pared with frames without thrombus (Table I in the Data Supplement). No difference was found in frame-level malapposition incidence (*P*=0.75), whereas malapposition area was numerically higher in frames with thrombus, without reaching significance (1.54 mm2 [0–3.44 mm2] versus 0.44 mm2 [0.00–6.70 mm2]; *P*=0.18).

Patient-Specific Substrates of Thrombosis

Tables II and III in the Data Supplement present patient-specific clinical, procedural, angiographic and OCT characteristics in BVS thrombosis.

(Sub)acute Thrombosis

In (sub)acute scaffold thrombosis, suboptimal implantation was the main mechanism. Incomplete lesion coverage was observed in three patients (Figure I in the Data Supplement), either because of mismatch of the pre-dilated segment and the scaffolded segment or because of incomplete coverage of the thrombosed segment in ST-segment–elevation myocardial infarction (Figure 1). In 2 cases with BVS implantation in ostial left anterior descending artery, angiography demonstrated scaffold protrusion into left main suggesting malapposition, also with underexpansion in one. Finally, in 1 case, thrombus was observed in a long overlap segment (7 mm by OCT), together with compact fibrin and Zahn-lines in aspirate histology (Figure 2), despite good expansion and apposition. In metallic stents, (sub)acute thrombosis was attributed to edge dissections in 3 cases, strut protrusion into left main with associated malapposition in 1 case, and extensive under- expansion in 1 case (minimal stent area, 1.19 mm2). In 1 case, there were no findings suggesting suboptimal implantation, but there was suspicion of poor compliance with DAPT.

(Very) Late Thrombosis

In 1 case, despite meeting Academic Research Consortium criteria for definite thrombosis, OCT disclosed the absence of thrombus and occlusive edge restenosis as substrate (Figure II in the Data Supplement). In most patients, (very) late BVS thrombosis was

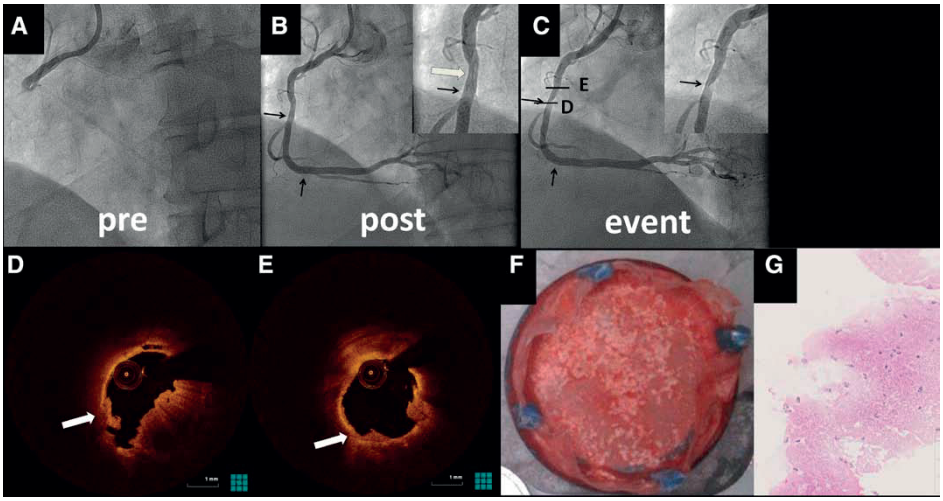

Figure 1 Acute thrombosis because of incomplete lesion coverage.
A, Preprocedural and (B) postprocedural angiogram after bioresorbable vascular scaffold implantation in a ST-segment–elevation myocardial infarction patient undergoing primary percutaneous coronary intervention. Mild haziness at the proximal edge postprocedure (arrow). C, Angiogram at event after thrombus aspiration. Red and white thrombus at the proximal scaffold segment (D) and proximal edge segment (E) extending >5 mm. The thrombus is overlying a thin-cap fibroatheroma, with possible rupture (arrow). Thrombus aspirate histology (F and G) demonstrates platelet-rich thrombus.

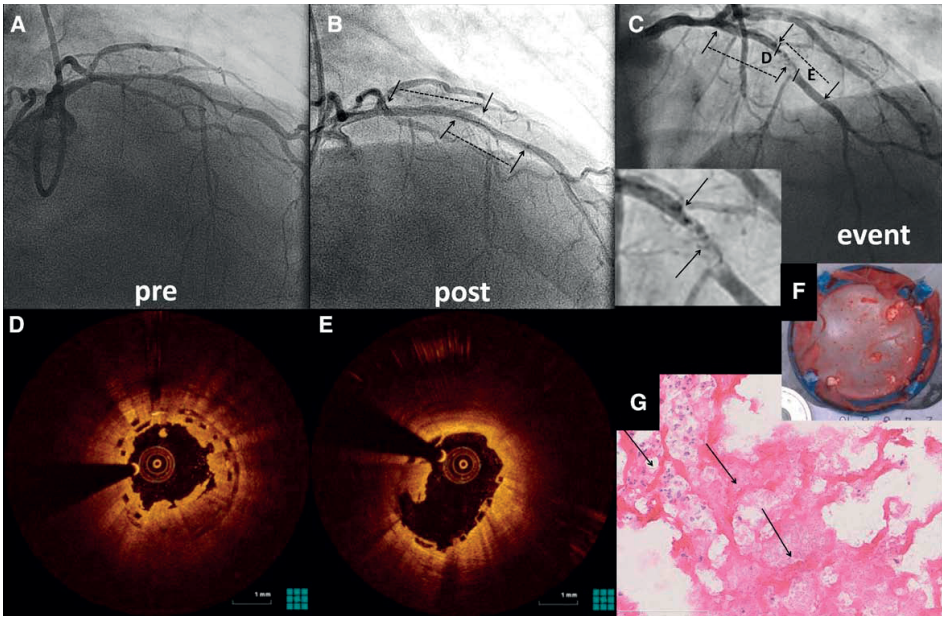

Figure 2 Subacute bioresorbable vascular scaffold thrombosis in extensive strut overlap.
A, Preprocedural and (B) postprocedural angiogram at baseline. C, Angiogram at event showing contrast deficit in the scaffolded segment. D and E, Optical coherence tomography demonstrates thrombus mainly at the overlap (D). F and G, Thrombus aspirate histology shows compact fibrin with Zahn-lines (arrows).

Table 2. Angiographic and procedural characteristics at baseline implantation

Angiographic characteristics	n=14
Vessel	
LAD n,(%)	9(64.3)
RCA n,(%)	2(14.3)
LCX n,(%)	3(21.4)
Bifurcation	3(21.4)
Ostial LAD/LCx lesion	6(42.9)
AHA/ACC classification	
A/B1	3(21.4)
B2/C	11(78.6)
Pre-procedure	
TIMI flow grade n,(%)	
0	5(35.7)
1	0(0)
2	1(7.1)
3	8(57.1)
Total occlusion (n=5)	
RVD, mm	2.98±0.22
Non-total occlusion (n=9)	
RVD, mm	2.61±0.35
Minimal lumen diameter, mm	0.94± 0.26
Diameter stenosis, %	64.1±9.8
Lesion length, mm	22.08±10.78
Post-procedure	
TIMI flow grade n,(%)	
0	0(0)
1	0(0)
2	0(0)
3	14(100)
RVD, mm	2.68± 0.33
Minimal lumen diameter, mm	2.32±0.26
Diameter stenosis, %	13.0±6.4
Dissection n,(%)	2(14.3)
Side-branch occlusion	1(7.1)
Procedural data	
Pre-dilatation n,(%)	13(92.9)
Post-dilatation n,(%)	7(50.0)
Thrombus aspiration n,(%)	4(28.6)
OCT guidance n,(%)	5(35.7)
Overlap n,(%)	3(21.4)

Table 2. Angiographic and procedural characteristics at baseline implantation (*continued*)

Angiographic characteristics	n=14
Bifurcation scaffolding	
T-stenting n,(%)	1(7.1)
Balloon dilation of side-branch ostium n,(%)	1(7.1)
Mean scaffolds per patient, n	1.36±0.63
Total scaffold length per patient, mm	28.57±14.56
Mean scaffold diameter per patient, mm	3.18±0.27

All values presented as n(%) or mean±SD. Abbreviations: RVD=reference vessel diameter; OCT=optical coherence tomography

Table 3. Angiographic characteristics at BVS thrombosis

Angiographic characteristics	n=14
TIMI flow grade, n,(%)	
0	10(71.4)
1	1(7.1)
2	2(14.3)
3	1(7.1)
Thrombus burden index, n,(%)	
0	0(0)
1	0(0)
2	1(7.1)
3	3(21.4)
4	0(0)
5	10(71.4)
Total occlusion (n=10)	
RVD, mm	2.94±0.30
Non-total occlusion (n=4)	
RVD, mm	2.23±0.65
Minimal lumen diameter, mm	0.86±0.18
Diameter stenosis, %	58.5±16.9

All values presented as n(%) or mean±SD. Abbreviations: RVD=reference vessel diameter

observed in the presence of regional suboptimal flow conditions, such as strut malapposition, scaffold fracture, and underexpansion. Four of 7 patients with (very) late BVS thrombosis undergoing OCT had malapposed struts. In 2 patients, malapposition was observed in the absence of scaffold discontinuity (Figure 3), also with underexpansion and restenosis in one of them. In the other 2 patients, malapposition was observed because of strut discontinuity: 1 with late discontinuity and intraluminal thrombus, 19 possibly resulting from balloon dilation of the scaffolded segment after the index

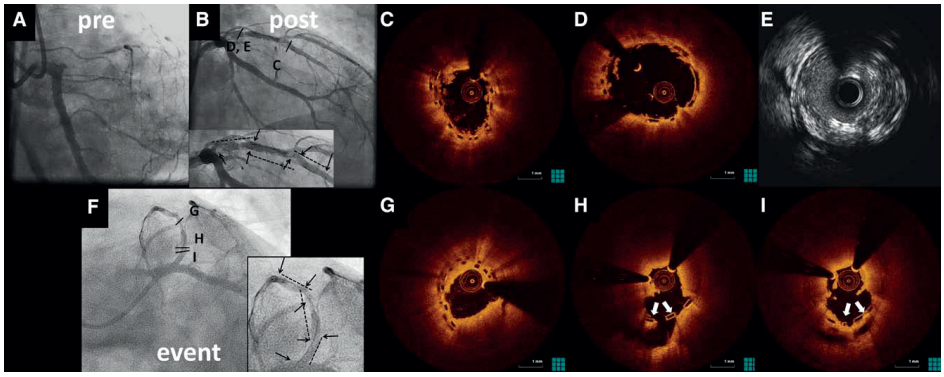

Figure 3 Late bioresorbable vascular scaffold (BVS) thrombosis and malapposition.
BVS implantation in a total left anterior descending artery occlusion with post-dilation (A), resulting in acceptable angiographic result with mild haziness (B), but residual thrombus by optical coherence tomography (OCT; C and D) and residual plaque burden by intravascular ultrasound (E). Post-dilation was not repeated, considering the risk of side-branch occlusion. F, Angiogram at event after thrombus aspiration. G through I, OCT shows massive red thrombus, and late malapposition (arrows).

procedure, whereas acute fracture had been detected in a second case. In this second case, late thrombosis occurred 2 days after both aspirin and clopidogrel discontinuation; however, there was no thrombus in the fracture site, but in an under expanded long overlap segment (Figure 4). In 3 cases, the substrate was not clearly identified: 1 very late thrombosis case where late discontinuity was suspected but not clearly identified because of thrombus (Figure III in the Data Supplement), 1 very late thrombosis case with extensive baseline malapposition (8.6% malapposed struts) and intra-scaffold dissections (no imaging at the event), and 1 late thrombosis case with T-stenting with BVS in a left anterior descending artery- diagonal bifurcation. The 2 latter patients were not receiving any antiplatelet agent at the time of late scaffold thrombosis. In metallic stents, late thrombosis was associated with malapposition in 2 cases and with strut protrusion into left main in another case. Complete DAPT discontinuation was confirmed in an additional patient and suspected in another with late thrombosis. In 4 patients with

Table 4. Optical coherence tomography findings in frames with and without thrombus

	Frames with thrombus (n=140)	Frames without thrombus (n=112)	p-value
Lumen area, mm^2	4.35(2.61-6.08)	5.84(4.11-7.58)	0.001
Scaffold area, mm^2	7.63(6.32-8.95)	8.14(6.83-9.46)	0.001
Malapposition area, mm^2 (n=16)	1.54(0-3.44)	0.44(0.00-6.70)	0.182
Frames with malapposition, %	7.6(0.0-16.2)	8.9(0.2-17.6)	0.752
Frames with overlap, %	8.3(1.5-15)	3.5(0.0-10.4)	0.196

All values presented as estimated marginal means (95% confidence intervals).

very late metallic stent thrombosis, baseline or follow-up angiography did not suggest any mechanical issues, while intravascular imaging was not performed.

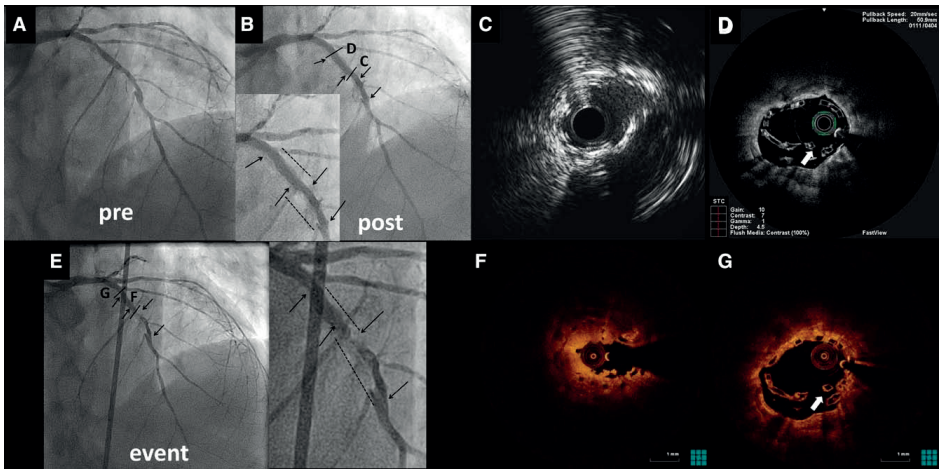

Figure 4. Late scaffold thrombosis after dual antiplatelet therapy discontinuation in overlapping bioresorbable vascular scaffold (BVS) with underexpansion. Overlapping BVS implantation in a diffuse calcified left anterior descending artery lesion (**A**), with acceptable angiographic result (**B**), but underexpansion by intravascular ultrasound (**C**), and scaffold fracture at the proximal edge by optical coherence tomography (OCT; **D**), possibly because of deep catheter intubation. The patient experienced late thrombosis 161 days post implantation (**E**), 2 days after aspirin and clopidogrel discontinuation. OCT shows thrombosis mainly at the overlap region, with low minimal scaffold area (4.21 mm2; **F**), whereas the fracture site remains free of thrombus (**G**).

DISCUSSION

This real-world case series provides unique insights in the mechanisms of BVS thrombosis. The main findings of our study are (1) device thrombosis remains an issue with BVS, with the timing of the event evenly distributed from acute to very late thrombosis; (2) similar to metallic stents, acute and subacute BVS thrombosis is predominantly associated with suboptimal implantation; and (3) late and very late scaffold thrombosis is frequently observed in the presence of regional suboptimal flow conditions, often in combination with cessation of DAPT.

Notwithstanding promising results from first-in-man studies showing favourable BVS long-term healing response 4, 7 and clinical results comparable with metallic DES, 5, 6 little is known about vascular healing after BVS implantation in complex lesions. Real-world registries have reported high 6-month BVS thrombosis rates, driven mainly by increased early thrombosis, 8, and 9 implying a possible role of suboptimal implantation. In our series, we report on 14 cases of definite BVS thrombosis at different intervals since implantation and compare the imaging findings with a control group of metallic

stents with definite stent thrombosis from the same time period, thus providing imaging insights into this complication. Importantly, suboptimal implantation was identified in both groups in a similar extent, suggesting that achieving an optimal implantation result might be more crucial than the type of implanted device in avoiding device thrombosis.

(Sub)acute BVS Thrombosis: Impact of Suboptimal Implantation

In acute and subacute BVS thrombosis, suboptimal implantation, comprising incomplete lesion coverage, malapposition, and underexpansion, was identified as the leading morphological substrate. This finding is in line with established substrates for metallic stent thrombosis12 and confirmed by observations in our control group. As the current BVS generation has a relatively high crossing profile, BVSs require rigorous lesion preparation, potentially translating to higher risk for incomplete coverage of the injured segment, compared with direct stenting often applied with metallic stents. Thus, our findings might urge the operator to specifically ensure complete cover- age of the lesion and injured segments, including angiographically apparent edge dissections.

Furthermore, the development of acute and subacute BVS thrombosis in 2 ST-segment–elevation myocardial infarction patients, after BVS implantation in ostial left anterior descending artery with scaffold protrusion into the left main, raises speculation that hemodynamic disturbances resulting from the protrusion and the associated malapposition could be a substrate for thrombosis.20–22 This was also documented by OCT in 2 metallic stent thrombosis cases, suggesting a similar contribution of this mechanism.

Finally, 1 case of subacute thrombosis occurred despite good expansion and apposition, in the presence of long strut overlap. The high strut thickness of Absorb BVS (150 μm) and bench observations of increased thrombogenicity of thick-strut stents which is more pronounced at overlap sites, 21 together with histological observations of Zahn-lines in the aspirates, indicate a potential involvement of flow disturbances induced by long overlap and make a case for minimizing over- lap length in treatment of long lesions by BVS. Whether this increased strut thickness could translate to increased thrombogenicity in vivo in the presence of an optimal implantation result remains unknown.

These findings underscore the significance of a meticulous BVS implantation technique, potentially including invasive imaging guidance, which has proven advantages over angiography for achieving optimal lesion treatment, in terms of coverage and expansion.23 It is important however to note that imaging guidance during the procedure might drive the opera- tor to excessive post-dilation, potentially leading to scaffold fracture. Therefore, thorough lesion evaluation before implantation might help avoid situations with pronounced mismatch between scaffold and artery size.

Late and Very Late BVS Thrombosis: Prominent Role of Suboptimal Flow Conditions

(Very) late thrombosis events in our series were attributed to factors potentially affecting flow conditions. These include underexpansion and pronounced strut protrusion into the lumen as a result of malapposition, bifurcation intervention, or strut discontinuity. Underexpansion has been identified as an important predictor of metallic DES thrombosis.3, 12 the significance of optimal expansion in avoiding BVS thrombosis is underscored by the finding of lower scaffold area in sites with thrombus compared with sites without thrombus.

The role of malapposition in late metallic DES thrombosis is debated 24; however, there is high prevalence in patients with events,1 and late malapposition in first-generation DES has been identified as predictor of very long-term adverse outcome.25 In our series, malapposition in (very) late BVS thrombosis (1.9±2.2%) did not differ significantly from late metallic stent thrombosis and was higher than the range reported for follow-up of second-generation metallic DES.26 Likewise, malapposition distance (486 ± 225 μm) was similar to metallic stents (265 ± 151 μm) and at the range of previously reported values in metallic DES thrombosis (mean: 350 μm).1 Therefore, malapposition of such extent, either persistent or late-acquired, might contribute to (very) late scaffold thrombosis.

As opposed to metallic DES, extensive malapposition in BVS might also result from strut discontinuity, which was associated with extensive thrombosis in a very late event in our series, possibly triggered by DAPT cessation.19 Whether small discontinuities, resulting from normal scaffold resorption, are associated with thrombosis is unclear. Notwithstanding this poorly documented association of discontinuity with thrombosis,18 precautionary measures such as respecting the post-dilation limits and cautious catheter recrossing or reintervention at later time points should be considered.

Role of DAPT Discontinuation

In addition to suboptimal implantation, DAPT cessation seems to play a role in BVS thrombosis, as in metallic DES.27 In 3 cases, there was a close temporal association of DAPT cessation with clinical manifestation of BVS thrombosis, tracking with observations in first-generation metallic DES, where scheduled P2Y12 inhibitor withdrawal was associated with increased ischemic events.28 As we assume concomitant suboptimal flow conditions in these patients, caused by underexpansion or extensive malapposition, we speculate on a possible synergistic effect of these factors in scaffold thrombosis. Consequently, these observations might raise questions about the need for platelet reactivity testing in patients with complex procedures or where optimal expansion cannot be achieved. Furthermore, the impact of DAPT cessation could be more pronounced when both aspirin and P2Y12 inhibitor are with- drawn in patients receiving chronic oral anticoagulation, as in 3 patients in our BVS series. Therefore, considering our observa-

tions of ongoing thrombotic risk even beyond 1 year, BVS implantation in such patients should be accompanied by adequate antiplatelet therapy or avoided in case of high bleeding risk.

Clinical Implications

Collectively, our findings underscore the significance of an optimal implantation result for minimizing the incidence of BVS thrombosis. Intravascular imaging at baseline could allow for early recognition and treatment of incomplete lesion coverage, better procedural planning in ostial lesions, 29 and optimal BVS sizing and post-dilating, thus avoiding underexpansion 23 or scaffold fracture. Moreover, similar to metallic DES, proper DAPT administration must be emphasized.27 Therefore, future studies should focus on optimal DAPT duration in patients with BVS, whereas platelet reactivity testing might be considered in selected patients with suboptimal implantation or complex intervention. Finally, in patients concomitantly receiving anticoagulants, administration of at least 1 antiplatelet agent until resorption or for life should be considered, pending appropriate studies.

LIMITATIONS

This study is focusing on a mechanistic understanding of BVS thrombosis. The study design and its single-centre nature preclude firm estimations of BVS thrombosis incidence and predictors in real-world populations, considering the inclusion of patients treated for BVS thrombosis in our centre, leading to possible underestimation. As OCT was not systematically performed, it was only available for 9 of 14 patients. Rou- tine OCT use could have provided further insights into the pathomechanisms of BVS thrombosis, whereas the small number of patients undergoing OCT might be a limitation in the mixed model analysis of OCT variables. Moreover, the lack of a control group of BVS without thrombosis precludes assessment of morphological predictors of BVS thrombosis. Residual thrombus might have underestimated our results, hampering complete substrate visualization, while precluding coverage assessment, which is based on thickness measurements for BVS, that are inaccurate in the presence of attached thrombus, rather than on visual confirmation of overlying tissue as in metallic stents.1, 7 Therefore, a possible contribution of incomplete strut coverage could not be systematically evaluated. Finally, no platelet function tests were performed that could evaluate a possible contribution of increased platelet reactivity to BVS thrombosis.

CONCLUSIONS

Suboptimal implantation with underexpansion, malapposition, and incomplete lesion coverage comprised the main pathomechanisms for both early and late BVS thrombosis in our series, similar to metallic stent thrombosis. DAPT discontinuation seems to also be a secondary contributor in several late events. Our observations suggest that a number of potential triggers for BVS thrombosis could be avoided and might warrant prospective validation.

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Supplemental Material

METHODS

Quantitative coronary angiography

Quantitative coronary angiography was performed using CAAS 5.11 (Pie Medical Imaging, Maastricht, Netherlands) and included reference vessel diameter (RVD), diameter stenosis (DS%), and minimal lumen diameter (MLD).

Histopathological analysis of thrombus aspirates

Thirteen patients underwent thrombus aspiration. Aspiration samples were successfully retrieved in four (30.8%) and were collected after filtering (40µm cell strainer BD Biosciences), snap-frozen and stored at -80°C. Macroscopic characteristics such as color, size and number of particles were documented. The frozen samples were cryosectioned (5µm serial sections), fixed with buffered paraformaldehyde 4%, and stained with hematoxylin-eosin as a routine stain, rosorcin-fuchin as an elastin stain and alcian blue for proteoglycans. Polarized light was used to detect birefringence.

RESULTS

Histopathological findings of thrombus aspirates

Four thrombus specimens were submitted for histopathology analysis. One sample did not contain any thrombus. One case contained only micro-thrombi [mean length 36µm (25-52µm)] without cellular elements. Two cases contained overt thrombi: one being platelet-rich and one containing compact fibrin with Zahn-lines. Eosinophilic granulocytes were observed in both but comprised <10% of all granulocytes, reflecting normal distribution. There was no evidence of hypersensitivity towards scaffold material. Vessel wall components and atheroma were not observed. There was no birefringence indicative of polymeric scaffold material in the aspirates.

Treatment of BVS thrombosis

Seven of 14 patients were treated by implantation of a metallic DES. Two patients with acute thrombosis due to edge problems were treated by additional BVS implantation. Four patients were treated by combination of thrombectomy and balloon dilation, while in one patient the attempt for treatment of acute thrombosis failed. This patient developed a large myocardial infarction (CK_{peak}: 4358U/L), which led to poor left ventricular

Table 1. OCT findings at scaffold thrombosis

OCT findings	n=9
Analyzed struts, n	208±145
Minimum lumen area, mm^2	2.26±1.56
Mean lumen area, mm^2	5.00±2.21
Minimum scaffold area, mm^2	6.21±1.20
Mean scaffold area, mm^2	7.88±1.42
Ratio of minimum scaffold area to reference area	0.93±0.20
Ratio of minimum scaffold diameter to nominal diameter	0.87±0.06
Malapposition area, mm^2 (n=3)	0.184±0.181
Mean neointimal/attached thrombus area, mm^2	1.99±0.78
Mean non-attached thrombus area, mm^2	0.017±0.028
Malapposed struts, %	2.8(1.5-4.1)
Malapposition distance(μm)	348(214-482)
Scaffolds with at least 1 malapposed strut, n,(%)	5(55.5)
Scaffolds with >5% malapposed struts, n,(%)	2(22.2)
Thrombus n,(%)	8(88.8)
Scaffold discontinuity n,(%)	2(22.2)

Values presented as n(%) or mean±SD. Malapposed struts and distance presented as estimated marginal mean (95% confidence intervals). Abbreviations: OCT=optical coherence tomography

systolic function and implantation of an implantable cardioverter-defibrillator for non-sustained ventricular tachycardia. In all patients, antiplatelet therapy after thrombosis was recommended for at least one year, continued by aspirin alone, including patients concomitantly receiving oral anticoagulation.

Outcome after treatment of BVS thrombosis

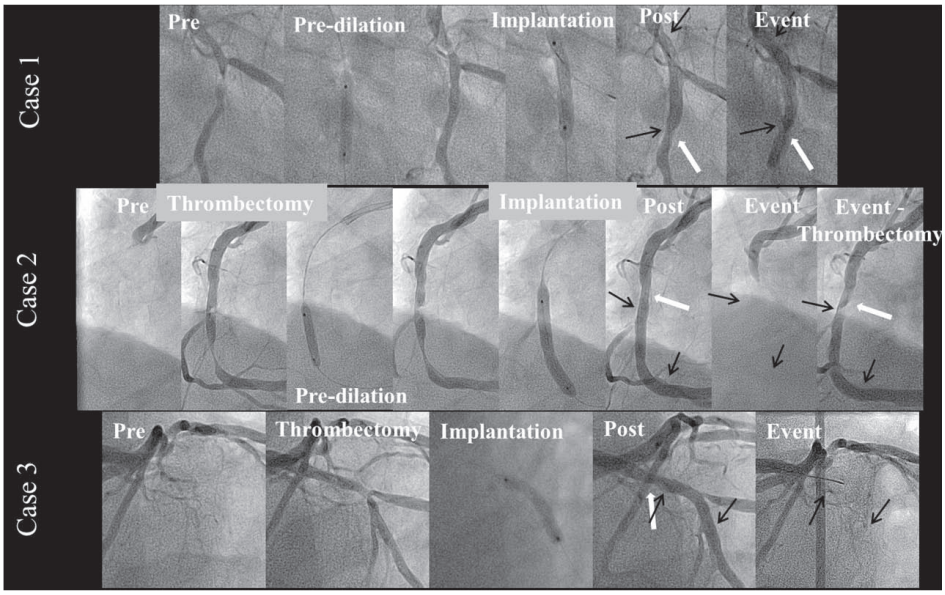
In 11 patients, follow-up was uneventful, while 3 patients suffered a recurrent event: One patient died of cardiac cause 4 days after the procedure. Another patient receiving a metallic DES for the treatment of BVS thrombosis, had an invasive follow-up 6 months after the thrombosis. OCT showed an overall good healing result with nevertheless sporadic clusters of uncovered struts. This patient suffered recurrent thrombosis, one year after the initial event, and 5 days after scheduled prasugrel discontinuation. Another patient had a repeat target vessel revascularization 4 months after thrombosis by coronary artery bypass graft (CABG), due to restenosis of the metal DES implanted for the treatment of BVS thrombosis.

Table 2. Patient-level characteristics

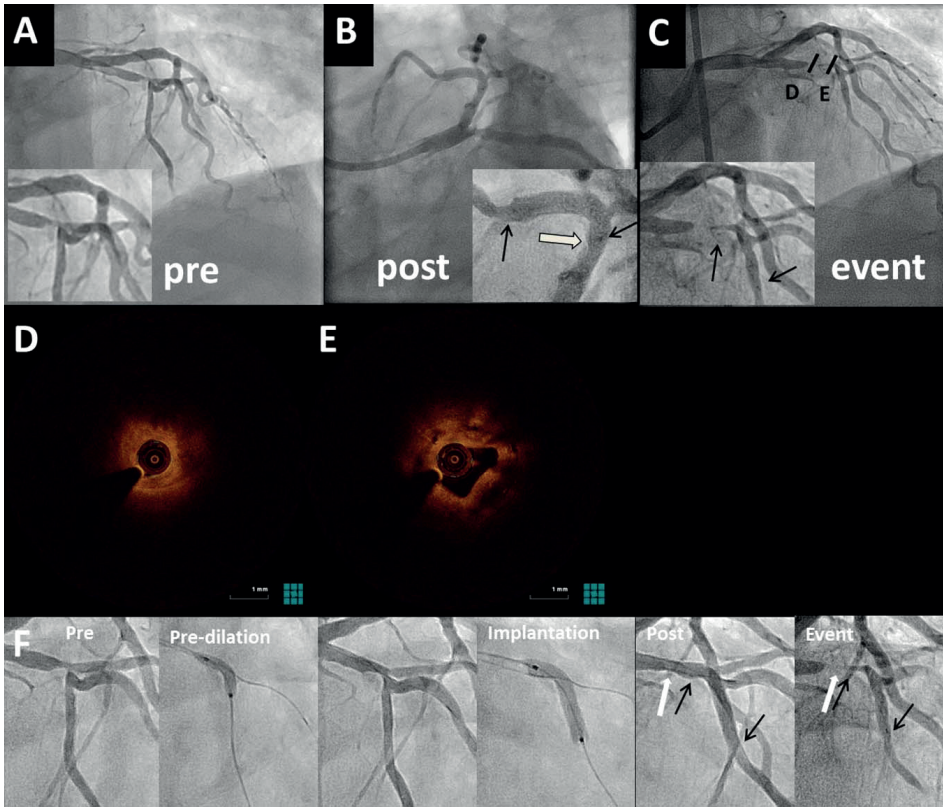
					Baseline and procedural characteristics								Scaffold thrombosis				
Case	Age	ACS	Prescribed P2Y12 inhibitor	Treated vessel	AHA/ ACC class	Bifur-cation	Ostial LAD/ LCx lesion	No of BVS	Total BVS length	OCT guided	Pre-dil	Post-dil	Type	Time (days)	ASA	P2Y12 inh	OAC
1	50	Yes	clopidogrel	LCX	C	-	-	1	18	-	+	-	Acute	0	+	+	-
2	51	Yes	ticagrelor	RCA	B1	-	-	1	28	-	+	-	Acute	0	+	+	-
3	59	Yes	prasugrel	LAD	C	-	-	1	18	-	-	-	Acute	1	+	+	-
4	62	Yes	prasugrel	LAD	B1	-	+	1	18	-	+	-	Acute	1	+	+	-
5	49	Yes	prasugrel	LAD	B2	-	+	1	18	-	+	+	Subacute	17	+	+	-
6	45	No	clopidogrel	LAD	B2	-	-	2	56	-	+	+	Subacute	2	+	+	-
7	65	Yes	prasugrel	LAD	B2	+	-	1	18	-	+	+	Late	142	+	+	-
8	69	Yes	clopidogrel	LAD	C	+	+	3	64	+	+	+	Late	47	+	+	-
9	59	No	prasugrel	LAD	C	-	+	1	28	-	+	+	Late	112	+	+	-
10	55	No	clopidogrel	LCX	A	-	+	1	18	+	+	-	Very late	675	+	-	-
11	71	No	clopidogrel	LAD	C	-	-	2	36	+	+	+	Late	161	-	-	+
12	62	Yes	prasugrel	RCA	C	-	-	1	28	+	+	-	Very late	478	+	-	-
13	86	Yes	clopidogrel	LCX	C	-	+	1	28	+	+	-	Very late	371	-	-	+
14	60	No	clopidogrel	LAD	C	+	-	2	24	-	+	+	Late	129	-	-	+

Table 3. Patient-level angiographic and OCT findings

Case	Type	Time (days)	Incomplete lesion coverage	Malapposition	Re-stenosis	Discontinuity	Under-expansion	Other baseline findings	Other follow-up findings	Recent DAPT disconti-nuation	DAPT disconti-nuation <1y
1	Acute	0	+ (dissection)	N/A	-	-	-	-	-	-	-
2	Acute	0	+ (thrombosed segment)	Yes	-	-	-	-	-	-	-
3	Acute	1	+ (thrombosed segment)	N/A	-	-	-	-	-	-	-
4	Acute	1	-	Suspected (angio)	-	-	-	-	-	-	-
5	Subacute	17	-	Suspected (angio)	-	-	Suspected (angio)	-	-	-	-
6	Subacute	2	-	No	-	-	-	-	Thrombus overlying extensive overlap region (7mm)	-	-
7	Late	142	+ (dissection)	N/A	+ (edge)	-	-	-	Occlusive proximal edge restenosis- no thrombus	-	-
8	Late	47	-	Yes (late malapposition)	-	-	-	Residual plaque burden/ residual thrombus	-	-	-
9	Late	112	-	Yes	+	-	+	-	-	-	-
10	Very late	675	-	Yes (late malapposition)	-	Late discontinuity	-	-	-	+	-
11	Late	161	-	Yes (Fracture)	-	Fracture	+	-	Thrombus overlying underexpanded overlap region	+	+
12	Very late	478	-	Resolved	-	Possible late discontinuity	-	-	-	-	-
13	Very late	371	-	Yes (Baseline)	-	-	-	Extensive intra-scaffold dissections	-	+	-
14	Late	129	-	No	-	-	-	-	Uncovered struts protruding at the bifurcation	-	+

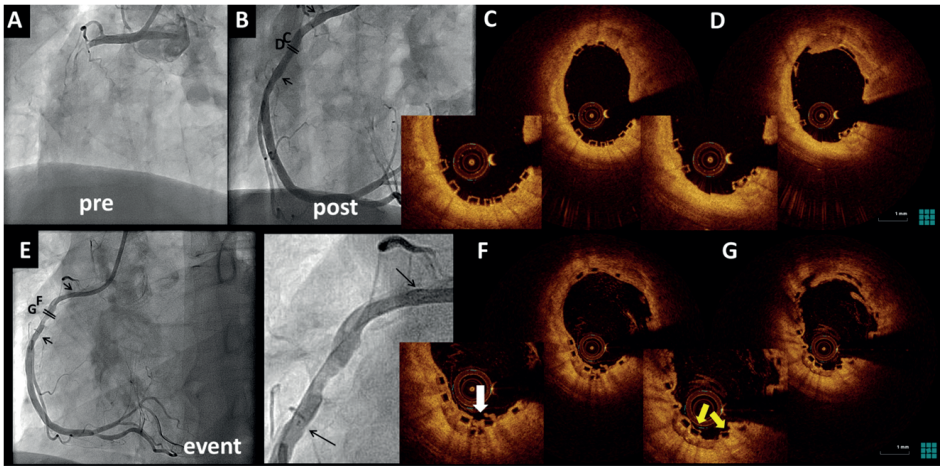


Supplementary Figure 1 Summary of the cases with acute thrombosis due to incomplete lesion coverage Black arrows indicate the scaffold markers and white arrows indicate the uncovered edge segment.



Supplementary Figure 2 Late stent thrombosis re-classified by OCT as edge restenosis resulting from incomplete lesion coverage.

A. Pre-procedural and B. post-procedural angiogram at baseline showing proximal edge dissection (white arrow). C. Angiogram at event (142 days) shows contrast deficit at the proximal edge, extending within the scaffold with TIMI I flow. OCT discloses occlusive edge restenosis (D) and restenosis within the scaffold with layered pattern (E), without luminal thrombus. F. Angiographic review demonstrating incomplete lesion coverage. Black arrows indicate the scaffold markers and white arrows the uncovered edge segment.



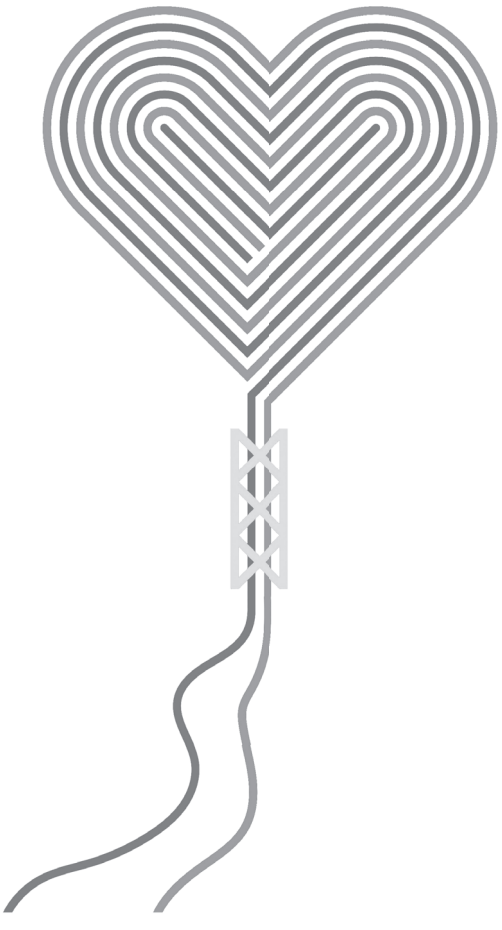
Supplementary Figure 3 Very late scaffold thrombosis without definite substrate.
BVS implantation in a proximal RCA lesion due to STEMI (A), with good post-procedural angiographic (B) and OCT (C-D) result. The patient suffered very late scaffold thrombosis 478 days post implantation, while only on aspirin (E). OCT shows suspected scaffold discontinuity (F; white arrow) and uncovered and possibly malapposed struts (G; yellow arrow) proximally to the thrombosed segment.

Chapter 12

Treatment of bioresorbable scaffold failure

CM Felix, BRC Everaert, N Jepson, C Tamburino, RJM van Geuns

Eurointervention. 2015 May 9



INTRODUCTION

Bioresorbable scaffolds (BRS) are a promising new interventional treatment strategy for coronary artery disease. They were developed to overcome some of the limitations of metal drug-eluting stents (DES), mainly the late reinterventions which occur at a consistent rate after one year and have not been reduced by use of local drug-elution. Initial experience in non-complex lesions established the efficacy in opening the vessel and the concept of bioresorption. However, with the use of BRS in more complex lesions, also the incidence of BRS failure, including both scaffold restenosis and thrombosis (ScT), has increased. Therefore, both understanding of the pathophysiology and of the available treatment options of scaffold failure remain important issues in insuring procedural and long-term clinical success.

Over the past years, bioresorbable scaffolds (BRS) have evolved as the new treatment strategy for coronary artery disease (CAD) with the Absorb bioresorbable vascular scaffold (BVS, Abbott Vascular, Santa Clara, California, USA) being the device most intensively studied.

A different CE marked scaffold, the DESolve myolimus-eluting bioresorbable coronary scaffold system (Elixir Medical Corporation, Sunnyvale, CA, USA) is currently under investigation. [1]. Although the DESolve is also PLLA based the degradation and drug-elution profile is different and different timings for failure strategies may apply. Recently, the Magmaris scaffold (Biotronik AG, Bülach, Switzerland. Previously known as DREAMS scaffold), a sirolimus eluting and magnesium based scaffold, received CE mark after its safety was tested in the BIOSOLVE-II first-in-man trial. [2] Resorption is faster than in PLLA based scaffolds. For both scaffolds, very little is known about the performance in real-world patients.

Invasive imaging at two years demonstrated that BVS are largely absorbed and late lumen enlargement occurred. In this way, BRS offer transient vessel support to prevent acute vessel recoil during angioplasty while eluting an antiproliferative drug to minimize neointima hyperplasia during the healing process. Multiple randomized controlled trials (ABSORB EXTEND, ABSORB II, ABSORB III, ABSORB China and ABSORB Japan) in non-complex patients showed results comparable to cobalt-chromium based everolimus eluting Xience V metal stent (CoCr-EES; Abbott Vascular, Santa Clara, CA, USA). [3-6] It should be underlined that only lesions of moderate complexity were included in these RCT's. In more real world lesion registries [7-13] BVS failure (including both scaffold thrombosis (ScT) and scaffold restenosis (Figure 1) occurs regularly and implantation of BVS in more complex patients seems to be associated with a higher rate of adverse events. In this chapter we will give a short overview of the pathophysiology and the treatment options in case of BRS failure.

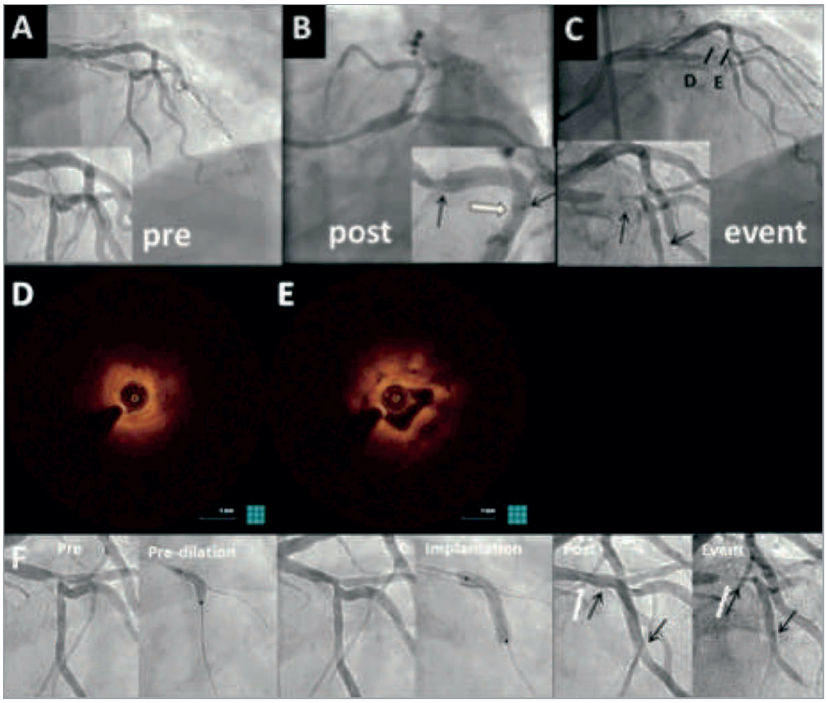


Figure 1 Edge restenosis treated with Absorb BVS.
A 65-year-old male patient presenting with an NSTEMI was treated with a 3.5×28 mm Absorb BVS for a trifurcation lesion of the LAD and two diagonals (A & B). He returned 142 days later for unstable angina due to a subtotal occlusion of the LAD with slow flow distal to the scaffold (TIMI 1) (C). OCT imaging revealed edge restenosis as the underlying mechanism for BRS failure (D) and restenosis within the scaffold with a layered pattern (E), but no luminal thrombus. The patient was treated with thrombus aspiration and a 3.5×38 mm DES (PROMUS™; Boston Scientific, Marlborough, MA, USA). A retrospective review of the post-procedural angiogram at baseline showed proximal edge dissection (B) and incomplete lesion coverage with geographic miss as the reason for restenosis (F series). Black arrows indicate the scaffold markers and white arrows the uncovered edge segment. Adapted from Antonis Karanasos et al; Angiographic and optical coherence tomography insights into bioresorbable scaffold thrombosis. A single-center experience. (Accepted and in press Circ Cardiovasc Interv 2015).

Risk factors for scaffold restenosis

The mechanism for BMS or DES restenosis is multifactorial and consists of stent recoil, formation of neointima, organization of thrombus, geographical miss and vessel remodeling. The pivotal factor in the process of ISR is neointimal formation, due to migration and proliferation of smooth muscle cells and myofibroblasts. In the long-term, metallic DES might fracture at hinging points in the coronary artery inducing an inflammatory reaction. Occasionally, some patients seem to be `limus` resistant and develop early restenosis (Figure 2). [14] Finally, negative remodeling of the vessel contributes to the restenosis process. [15]

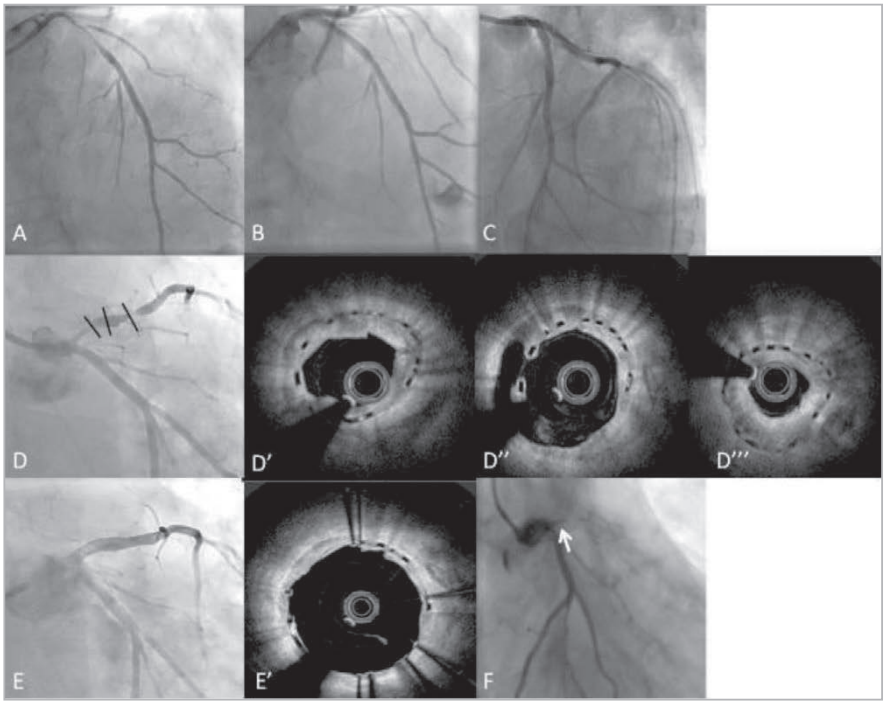


Figure 2 Absorb BVS and neointimal hyperplasia treated with DES, and recurrent failure.
A 59-year-old male patient was treated with one Absorb BVS (3.5×28 mm) in the proximal LAD for unstable angina (A-C). The patient developed an NSTEMI 112 days after the index PCI with TIMI 1 flow (D) and was therefore classified as a definite ST. OCT showed mild scaffold underexpansion (3 mm diameter) with severe neointima development (D' and D''') but also areas with late malapposition and potential vasodilatation and thrombus resorption (D''). Treatment consisted of thrombectomy, eptifibatide and a 3.5×32 mm DES (PROMUS; Boston Scientific) followed by post-dilatation with 4.0 mm balloon, the lumen increased significantly and malapposition was resolved on OCT (E') with good angiographic results (E) . The patient returned almost four months later with unstable angina. There was a severe ISR on angiography (F) with total occlusion (arrow) and collateral flows suggesting a resistance to the "limus" drugs used. It was decided to perform a semi-urgent CABG, which took place four days later.

The rates of BMS-ISR have been described to be as high as 60%, depending on several risk factors such as lesion complexity, patient co-morbidities and vessel size. [16-19] The use of DES has significantly reduced the rate of ISR, although DES-ISR rates at one year have been stated to occur in 3% - 20% of the patients, depending on DES generation and patient, lesion and procedural characteristics. [20]

Multiple patient, lesion and procedure-related risk factors for ISR in BMS and DES have been reported, including diabetes mellitus, multi-vessel disease, stent length, bifurcation lesions, small caliber vessels, chronic total occlusion (CTO), strut thickness, usage of multiple stents and stent underexpansion. Hypersensitivity reaction to the polymer is another important mechanism. ISR by itself is also a predictor for future ISR. [20-25]

Also the stent type plays an important role which can be related to strut thickness, drug dosage and drug release profile. In general, thicker stent struts cause more flow disturbances with reduced endothelial shear stress [26], which does enhance the process of neointimal hyperplasia.

It seems likely that most risk factors for ISR with BRS are the same as for ISR with BMS or DES; however, at this moment, there is little evidence to confirm this presumption. Recently, a case series reported on geographical miss and scaffold underexpansion as being the most frequent causes of BRS failure. [27]

Risk factors for scaffold thrombosis

Several risk factors for ST exist. Many of them are also predictive for stent restenosis. These risk factors can be categorized as lesion, patient and procedure-related factors. Procedure-related factors are stent malapposition, stent undersizing, dissection, placement of multiple stents, stent overlap and stent length. Lesion-related factors include coronary bifurcations, heavily calcified lesions, long lesion length, small vessel size and CTO. Finally, there are the patient-related factors such as diabetes mellitus, advanced age, renal failure, low ejection fraction, smoking, prior CABG, acute coronary syndromes (ACS) at presentation, (early) discontinuation of DAPT or resistance to clopidogrel. [28, 29]

Probably, and in line with DES, the rate of ScT varies depending on lesion, patient and procedure-related characteristics. The most remarkable difference between BVS and current DES is the increased strut thickness and width (comparable to old stainless steel BMS and first generation DES). This will increase the early uncovered surface significantly. Also, strut thickness induces convective flow patterns, triggering platelet deposition. [30] Susceptibility to platelet aggregation might further aggravated be in conditions such as scaffold underexpansion, treatment of thrombotic lesions, e.g. during ACS, and DAPT interruption.

Scaffold underexpansion is an important issue in BVS [31] and is an important contributor to BRS failure. It occurs less if lesions are treated using an optimal implantation strategy. Starting with the use of a non-compliant balloon with the same size as RVD and with a 1:1 ratio to the vessel, full expansion of the scaffold and with the same size as RVD and post-dilatation with a non-compliant balloon up to a maximum of 0.5mm larger. [32, 33] Discontinuation of DAPT and edge dissections have also been described as causes of Sct. [34] Currently ongoing and future all-comer, randomized controlled trials will indicate whether BRS have more favorable rates of late ScT compared to the current generation DES.

Scaffold dislodgement

In severely calcified or tortuous lesions, successful delivery of BRS can be difficult and the scaffold could be potentially dislodged [35] in the same way as metallic stents.

However after an early publication, no further cases of scaffold dislodgement have been reported anymore.

Incidence of scaffold failure in BVS studies and registries

Little is known about the exact incidence of ST and ISR with the use of BRS and in most publications the cause of BRS failure, whether by ScT or ISR, is not clearly reported.

The ABSORB II study reported a TLR rate at one year of 1% in the BRS group compared to 2% in the Xience group. [3] Twelve month TLR rate in ABSORB III was 3.0% (vs 2.5% in the Xience group). [5] The five year TLR rate in low risk patients and non-complex lesions of the ABSORB Cohort A study was 3.4% [36], whereas the TLR rate of an everolimus-eluting stent (EES, Xience V) at five years was 8.6% in the SPIRIT III trial. [37]

Wohrle et al. reported on the one year outcomes of the ASSURE registry: five cases of TLR (2.8%) occurred, all due to ISR. Treatment options used were DEB (two patients with long lesions in small vessels, treated with overlapping BRS), DES (ISR of a saphenous vein graft due to malapposition of the BRS), POBA (for incomplete (proximal) BRS expansion) and CABG (total occlusion of the target vessel). [8]

The GHOST-EU trial, including 1189 patients, showed a TLR rate of 2.5% at six 6 months and target lesion failure (TLF: a composite of cardiac death, target-vessel myocardial infarction or ischemia-driven target-lesion revascularization) rate of 4.4% at six months. In a multivariate analysis, TLF was seen more in patients with diabetes and in smokers, however this was not statistically significant. [7]

Ishibashi et al. summarized the rates of BVS ST reported in multiple trials. The incidence of ST varied from 0 up to 3.0% in a time period ranging from one to six months [38]. In another recent review article the number of definite ST ranged from 0% at one year to 3.2% at six months. [39]

Most cases of BRS-ST occur within the first 30 days after implantation; however some cases of late ST were also described. The cumulative incidence of ST at six months was 2.1% in the GHOST-EU trial. In 13% of the cases there was DAPT discontinuation. Other possible causes are the low rate of post-dilatation and little usage of invasive imaging in B2/C lesions. [7]

Regarding the first 450 patients enrolled in the ABSORB Extend trial, seven cases of BRS failure occurred, i.e. three cases (0.67%) of scaffold dislodgement and four cases of ST (0.89%). [35]

Of the 101 patients included in the BVS Cohort B trial, only six cases of ISR occurred (5%) during a three year follow-up period. The mechanisms for ISR were procedural edge injury during the initial procedure, geographical miss, and in one case myocardial bridging. In three cases the cause of ISR could not be identified. [40]

The BVS Expand single-center registry (excluding STEMI patients) reported a definite ScT rate at 18 months of 1.9% and a TLR rate of 4.0%. [9]The mid-term outcomes of the

BVS STEMI First registry (including only STEMI patients) showed a high rate of definite Sct (4.3%), mainly caused by procedural factors, and TLR (5.7%). [10]

The Amsterdam ABSORB registry, reporting on complex lesion (AHA/ ACC lesion classification B2/C in 67%), revealed a one-year TLR rate of 8.9% and 11.4% at two years. [13] One-year TLR rate from the Polish National Registry, including both stable and ACS patients, was 1.5%. [41]

Summarized, TLR rates can be as high as 8.9% at one year, depending on lesion and patient complexity. BRS failure can be caused by geographical miss, scaffold dislodgement, scaffold malapposition and underexpansion, lesion length and DAPT discontinuation.

How to treat BRS failure

Multiple treatment options for treating BRS failure exist: thrombus aspiration, balloon angioplasty (POBA), BMS, DES, BRS, drug-eluting balloons (DEB) or medical treatment (e.g. with a thrombolytic agent or a glycoprotein IIbIIIa inhibitor (GPI)). Deciding which is most suitable depends on the triggering mechanism and not infrequently multiple underlying factors are present. Understanding the fundamental pathophysiological mechanism underlying the TLF is of key importance to direct subsequent management. Invasive imaging modalities, such as optical coherence tomography (OCT) are of paramount importance to achieve treatment success. OCT enables the operator to determine between the different mechanisms for BRS-TLF such as scaffold underexpansion, scaffold malapposition or undersizing, geographic miss (edge dissection, edge restenosis), neointimal hyperplasia or scaffold strut fracture.

BRS thrombosis after DAPT interruption, whether acute (<24 hours,) subacute (<1 month) or late, can be managed with the use of thrombectomy, GPI and/or POBA. In patients on clopidogrel that present with an occlusion of the target vessel due to a thrombus, platelet function testing and switching to more potent P2Y12 inhibitor has to be considered.

Early underexpansion and malapposition can be treated with POBA with non-compliant balloons in a 1:1 balloon – vessel ratio and with sufficient diameter and pressure, although the maximum overexpansion limit of 0.5 mm always has to be respected for BVS, especially in the situation of undersizing (Figure 5). If the vessel is above 4 mm in diameter and there is serious malapposition, large metallic stents are indicated. Preferably a DES is used, although potentially a BMS could be sufficient for treatment of acute or subacute (<30 days) scaffold failure . However, the negative effects of an additional dose of antiproliferative drugs when DES are used seem only theoretical and hence not of clinical importance. If underexpansion cannot be managed by POBA alone, a BMS or DES is indicated to ensure additional radial support (Figure 3). To minimize stent overlap, only the insufficiently apposed areas needed be covered with the new stent. After thirty days we strongly recommend DES (or even second BVS in larger vessels) as the

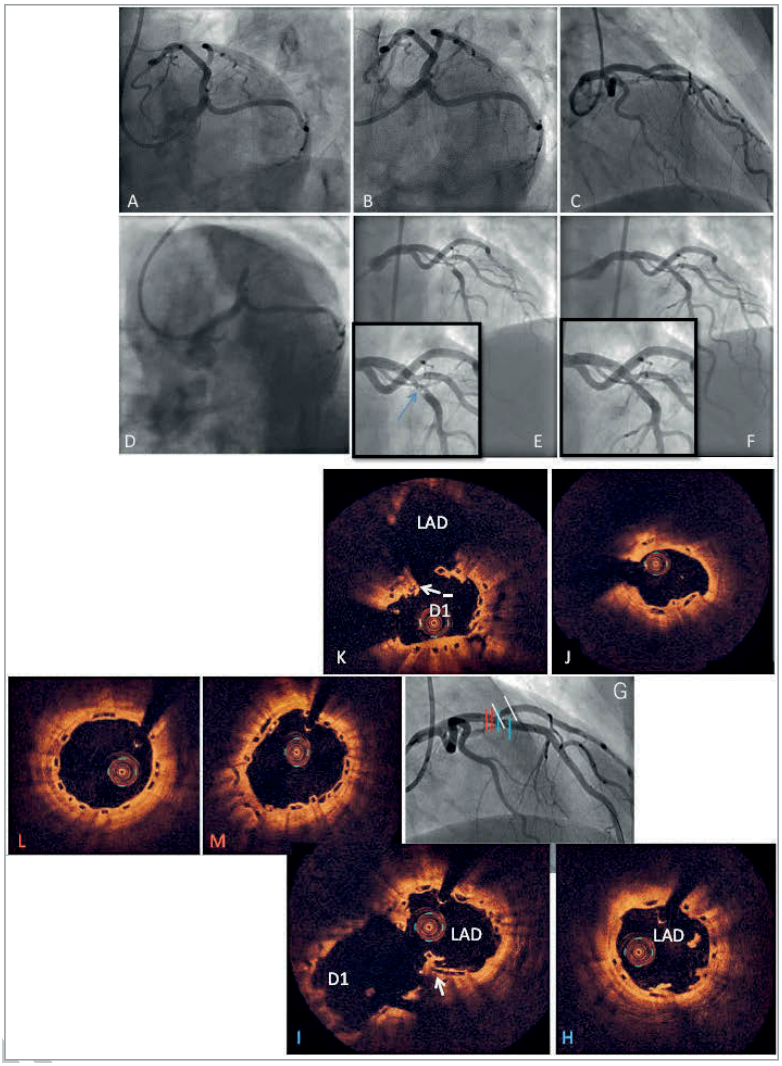


Figure 3 Absorb BVS failure due to discontinuation of DAPT treated with thrombus aspiration and POBA. A 60-year-old male patient with a history of smoking, hypertension and heart failure presented with stable angina. There was one-vessel disease and a LAD, 1 diagonal, lesion (Medina 0,0,1) on angiography. A) Two 3.0×12 mm Absorb BVS were placed in the LAD and 1st diagonal, using the T and protrusion technique with good results in the spider (B) and RAO (C) projections. After 129 days the patient developed a STEMI due to an occluded LAD (D) potentially due to ascal and prasugrel discontinuation for CVA. POBA with a 3.0 mm balloon was then performed. After three AngioJet (Boston Scientific) runs, the angiographic result was acceptable (E) and eptifibatide was continued for 24 hours. The treatment of BRS failure was reviewed four days later using OCT (F-M). Pullback from the LAD (lower row) showed some remaining thrombus (H), and signs of fractures or double layer of uncovered struts (I, arrow). Pullback from the diagonal branch showed some undersizing distal (J) and some double layer and lost struts (K, arrow). Proximal to the bifurcation the struts were well apposed and mainly well covered (L and M).

remaining dose of everolimus on the BVS might not be sufficient to effectively reduce neointimal hyperplasia (Figure 3). For undersizing, POBA could be sufficient up to six months as the goal is ensuring optimal apposition without further vessel dilatation (low pressure) inducing a new healing process.

After approximately six months the tie chains between the crystal polylactide lamellae become more and more hydrolyzed and the radial strength and subsequent vessel support gradually decreases (Figure 4). [42] BRS failure after six months due to mechanical problems will need placement of an additional stent or scaffold.

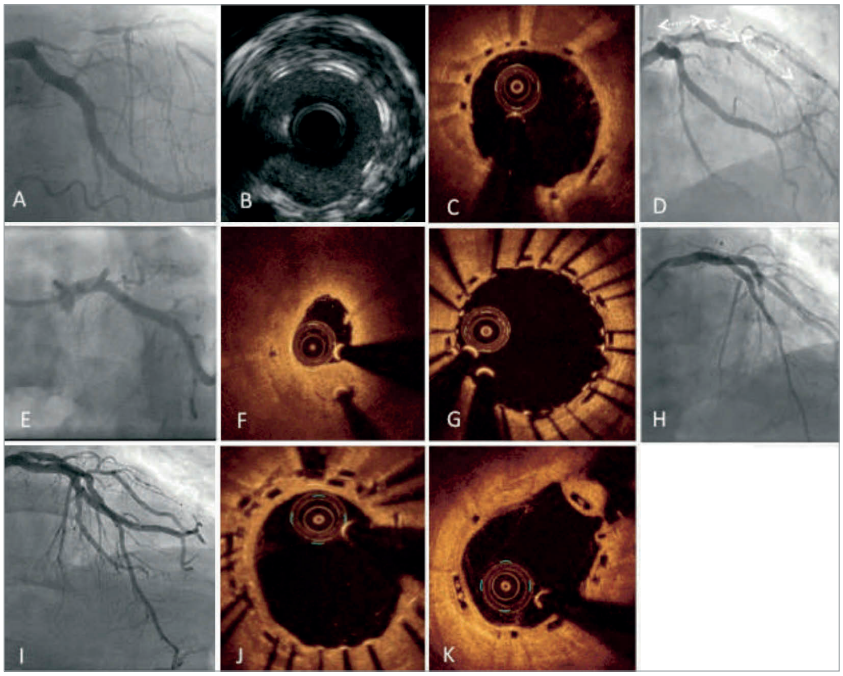


Figure 4 Scaffold thrombosis due to underexpansion treated with DES.
A 69-year-old male patient presented with an NSTEMI. Angiography showed one-vessel disease with long narrowing of the proximal and mid LAD and collateral filling (A). Three Absorb BVS (3.0×28 mm, 3.5×18 mm, 3.5×18 mm) were implanted (D). After placement of the first two scaffolds there was compression and thrombus in the 1 diagonal. Invasive imaging post procedure revealed organised thrombus behind the struts of the proximal scaffold (B: IVUS) and thrombus protrusion at the overlapping scaffolds (C: OCT). After 47 days the patient presented with a non-Q-wave myocardial infarction due to a full occlusion in the proximal LAD (E). There was some underexpansion, but a large thrombus on OCT (F). He was treated with thrombectomy, eptifibatide and PCI with a 3.5×38 mm DES (XIENCE) covering the proximal BVSs with a good angiographic and OCT result (G & H). The control diagnostic angiography made 110 days later (I) displayed good scaffold and stent apposition on OCT with good coverage of the struts of the new DES (J) and the untreated original distal Absorb BVS (K).

In the setting of a geographical miss leading to a clinically relevant acute or subacute edge dissection, a BRS bailout strategy could be used. In case of a geographical miss with apparent edge restenosis, placement of an additional BRS is possible although converting to DES with a minimal risk of repeat ISR is more prudent. ISR due to intimal hyperplasia can be treated by a DEB (<6 months) but after 6 months, additional vessel support is indicated (with a preference for DES) (Figure 1).

Lastly, in the case of limited scaffold strut fracture, POBA should be able to correct the malapposed segments [43]. For more extensive fractures or large diameter vessels, a new stent (BMS or DES) would be the treatment of choice. Again, after six months disintegration of the scaffold is initiated and additional radial strength is necessary (DES preferred). In case of both fracture and underexpansion, lesion dilatation is necessary and we recommend an additional DES from thirty days after the initial BRS placement. Treatment options for BRS failure are summarized in table 1.

Table 1. Treatment options for BRS failure.

	Acute (< 24 h)	Subacute (< 30 days)	Late (< 6 months)	Very late (> 6 months)
DAPT interruption	GPI/ thrombectomy/POBA			
Underexpansion	POBA		DES/ BVS	
Undersizing/ Malapposition	POBA: max 0.5mm > nominal > 4mm: DES/ BMS*			DES/ BVS
Geographical miss	Dissection: BVS bailout		Edge stenosis: DES/ BVS	
Neointimal hyperplasia	--		DEB	DES/ BVS
Strut fracture	POBA: max 0.5 > nominal > 4mm: DES/ BMS*			DES

*In the first period, as drug release is still ongoing, BMS theoretically should be sufficient

However, we have to mention that most of the clinical experience with BRS failure is gained from the experience with the Absorb BVS platform, and that, given the paucity of trial numbers, only few data are available for other BRS subtypes such as the DESolve novolimus-eluting bioresorbable coronary scaffold system (Elixir) or metal-based (magnesium) resorbable devices. As such, these recommendations for the treatment of BRS failure are only applicable to the Absorb BVS.

CONCLUSION

Treatment of scaffold failure should target any suboptimal result. After thrombus aspiration and aggressive medical treatment, intravascular imaging is advised to reveal any scaffold abnormalities. A wide range of strategies can be applied to correct suboptimal scaffold results. The major difference between BRS and DES in the treatment of target lesion failure is the more frequent need for additional vessel support (using a second BRS or a DES).

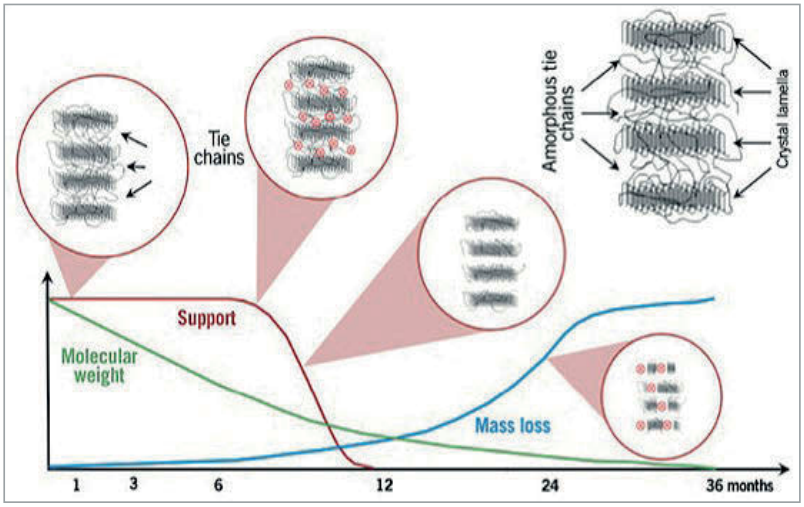


Figure 5 Bioresorption of Absorb BVS. Initially, cleavage of polylactides results in minimal molecular weight loss with remaining full support until six months.
After six months, degradation significantly impacted on tie chains between crystal lamellae occurs rapidly, reducing radial support when the material starts to become brittle. Implantation of additional vessel supportive therapy is indicated to successfully treat lumen reduction. Adapted from Serruys et al (34).

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Chapter 13

Very late scaffold thrombosis in Absorb BVS: association with DAPT termination?

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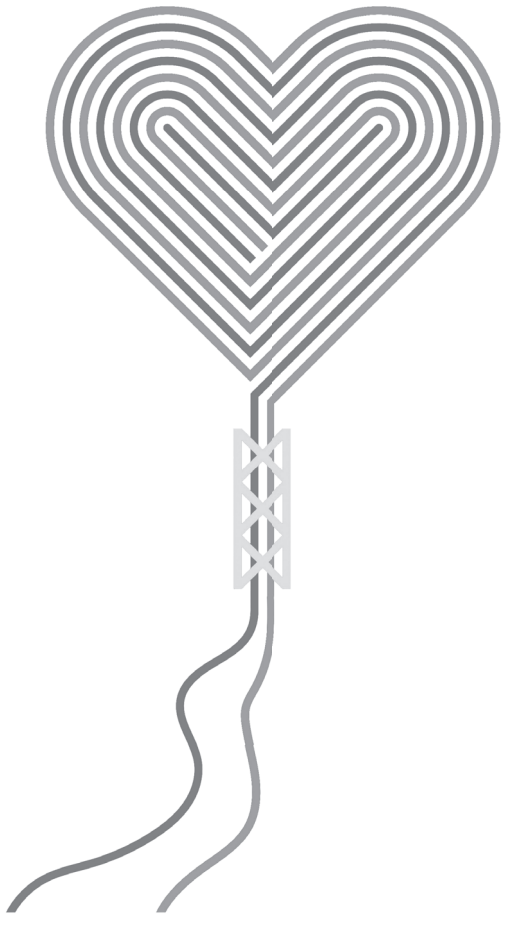

ABSTRACT

Objectives

To shed light on the occurrence of very late scaffold thrombosis (VLScT) in patients treated with the Absorb bioresorbable vascular scaffold (BVS) and the possible association with termination of dual antiplatelet therapy.

Background

Multiple studies have proven feasibility and safety of the Absorb BVS. However, more recently, concerns were raised regarding the higher incidence of VLScT.

Methods

A viewpoint was created by a brief description background literature and three VLScT case descriptions.

Conclusions

Based on our case series and previous publications, we encourage prolongation of DAPT beyond 12 months after implantation of BVS.

The Absorb bioresorbable scaffold (BVS, Abbott Vascular, Santa Clara, California, USA) is a new promising treatment option for coronary artery disease to overcome limitations of metal drug eluting stent and is widely investigated. [1] Lately, concerns were raised regarding the occurrence of very late scaffold thrombosis (VLScT) in patients treated with BVS. [2] The ABSORB II randomized controlled trial (RCT) reported a disturbing number of six VLScT in 335 patients at three years follow-up. None of these patients were using dual antiplatelet therapy (DAPT) at time of the event. [3] Two-years results of the ABSORB Japan RCT described 4 cases of VLScT; two out of four patients had terminated DAPT. [4] These findings stimulated us to investigate the occurrence of this very late event and its relation with DAPT termination.

In our daily practice of three regional centers, we also have encountered cases of VLScT after discontinuation of DAPT. At 18 months, three of the four VLScT in a cohort of 685 patients seemed to be closely related to DAPT discontinuation. These cases occurred within 35 days after DAPT termination, which we believe needs the attention of the medical community.

A 60-year old female with risk factors dyslipidemia, hypertension, history of percutaneous coronary intervention (PCI), presented with stable angina pectoris and angiography revealed one-vessel disease of the RCA. Treatment consisted of pre-dilatation, implantation of 3 overlapping BVS and post-dilatation. Patient was using aspirin and clopidogrel for 369 days. Ten days later, she presented with STEMI with visible thrombus on angiography, which was treated with thrombectomy, drug-eluting balloon and abciximab.

A 63-year old male without cardiac risk factors was admitted with a STEMI due to an occluded mid-LAD. After thrombectomy, he underwent primary PCI with 2 overlapping BVS and post-dilatation. Ticagrelor was stopped at day 381 days and 35 days thereafter, this patient presented with STEMI due VLScT. Intravascular imaging revealed clear thrombus and minimal malapposition. Thrombectomy, stenting with everolimus eluting stent, and post-dilatation were performed.

A 50-year old female with positive family history for CAD and a current smoker was admitted to the hospital with a STEMI. After thrombectomy and pre-dilatation, she underwent PCI of the RCA with 1 BVS. Post-procedural OCT revealed malapposition and therefore, post-dilatation with a 4.0 mm balloon was performed reducing malapposition but unfortunately not eliminating this. At day 449, twenty days after prasugrel was terminated, the patient returned with a Q-wave STEMI due to angiographically and OCT proven ScT and malapposition. Treatment consisted of rePCI with thrombectomy, balloon angioplasty and Gp IIb/ IIIa inhibitor.

These cases were reported to draw attention to a problem that is becoming more common: VLScT. In our cohort and in the ABSORB II trial, no VLScT occurred in patients continued DAPT for a longer period of time. Based on this experience and previous

publications [4], we encourage prolongation of DAPT beyond 12 months after implantation of BVS, likewise as has been demonstrated to be efficient for high-risk DES-treated patients with a low bleeding risk [5]. A DAPT score ≥ 2 seems optimal for current DES whereas an increased risk of ischemic events for first generation DES would warrant an additional point [6] and this could theoretically apply for first generation BVS. Extending DAPT even longer, to 30 months as investigated by the DAPT study in DES patients, will cover the majority of time period before the resorption process of BVS is completed. [7] More data and dedicated studies are needed to confirm this recommendation. We believe that, considering inherent difference between BVS and metallic stent, probably specific DAPT recommendation is warranted for patients receiving BVS.

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Chapter 14

Potentially increased incidence of scaffold thrombosis in patients treated with Absorb BVS who terminated DAPT before 18 months

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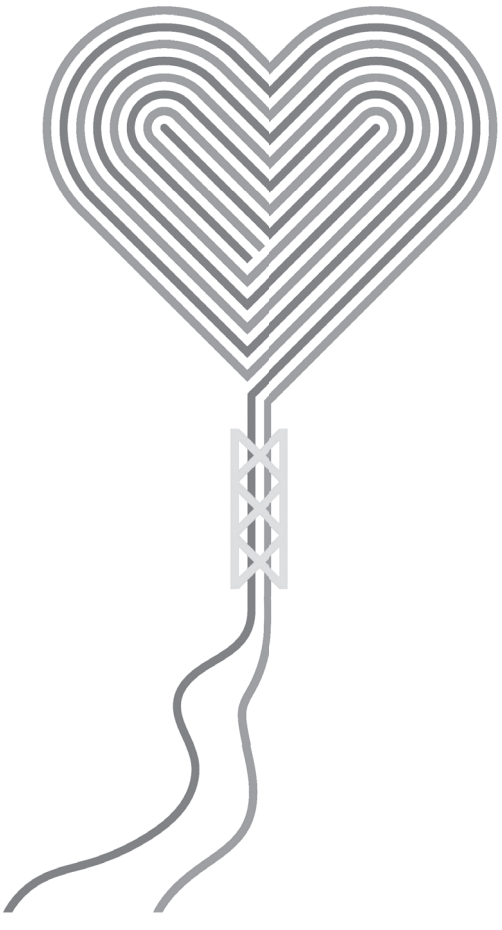

ABSTRACT

Aims

To investigate the impact of dual antiplatelet therapy (DAPT) termination on late and very late scaffold thrombosis (ScT) in patients treated with Absorb bioresorbable vascular scaffold (BVS).

Methods and Results

Data of registries of 3 centers were pooled (808 patients). To investigate the effect of DAPT termination on ScT after a minimum of 6 months, we selected a subgroup ('DAPT study cohort' with 685 patients) with known DAPT status > 6 months and excluded the use of oral anticoagulants and early ScT. In this cohort, definite/ probable ScT incidence for the period on DAPT was compared to ScT incidence after DAPT termination. ScT incidence was 0.83 ScT/ 100 py with 95% confidence interval (CI): 0.34-1.98. After DAPT termination, the incidence was higher (1.77/ 100 py; 95% CI: 0.66-4.72), compared to the incidence on DAPT (0.26/ 100 py, 95% CI: 0.04-1.86; p=0.12) and increased within the month after DAPT termination (6.57/ 100 py, 95% CI 2.12-20.38; p=0.01). No very late ScT occurred in patients who continued on DAPT for a minimum of 18 months.

Conclusion

Incidence of late and very late definite/ probable ScT was acceptable. Incidence was low while on DAPT but potentially higher when DAPT was terminated before 18 months.

INTRODUCTION

Bioresorbable scaffolds are the new treatment option for coronary interventions with the aim to overcome some of the limitations of metal drug-eluting stents (DES), such as very late stent thromboses (ST) and reinterventions due to polymer reactions, strut fracture, neoatherosclerosis and inflammation.

The Absorb bioresorbable vascular scaffold (BVS, Abbott Vascular, Santa Clara, California, USA) has been most intensively studied. Multiple meta-analyses, showed comparable one-year outcomes for target lesion failure (TLF) of BVS versus cobalt-chromium based everolimus eluting Xience metal stent (CoCr-EES; Abbott Vascular, Santa Clara, CA, USA) in selected patients. Numbers of scaffold thrombosis (ScT) and target vessel MI tended to be higher in BVS group. [1-3]_ENREF_2 In populations reflecting real-world patients [4-8], ScT occurs more frequent. More recently, concerns were expressed about the occurrence of very late (> 1 year) scaffold thrombosis (VLScT). [9, 10] In randomized controlled trials (RCT's), VLScT up to 2 years were low on one (1.6%) but higher in another (2.0%) at 3 years. [11, 12]

Dual antiplatelet therapy (DAPT) reduces the risk of local thrombotic events related to stent implantation, systemic thrombotic events, and cardiovascular mortality. In the current ESC and AHA/ ACC guidelines, a minimum DAPT duration of 6 months after DES implantation is recommended, with prolonged treatment in patients with an increased risk for thrombotic events and low bleeding risks. For BVS, the optimal DAPT duration is not yet clearly defined. [13, 14] The early studies investigating BVS applied a minimum DAPT duration of 6 months. In the more recent RCT's, a minimum duration of 12 months was implemented. [11, 15]

To summarize, data on long-term ScT outcomes after BVS implantation in real-world patients is lacking and information on optimal DAPT duration missing. To fill the gap, we describe the incidence of ScT and investigated the impact of DAPT termination on late and very late ScT in regular clinical practice.

METHODS

Population

Patients were pooled from registries of 3 Dutch centers where the Absorb BVS was used as part of daily clinical practice. The decision to treat a patient with BVS was made at the discretion of the interventional cardiologist.

The patients of the Erasmus Medical Center were derived from two investigator-initiated, single-center, single-arm registries (BVS Expand and BVS STEMI). In- and exclusion criteria have been described elsewhere. [5, 6] Patients included in the two other hospital

registries were part of local all-comers registries initiated for the control of quality of standard care following introduction of a new CE approved device.

Between September 2012 and April 2015, 808 patients treated with at least one BVS were included in this study (total cohort). To investigate specifically the association between DAPT and late events without interference of oral anticoagulants, the DAPT cohort was selected by including patients with a known DAPT status and with duration of at least 6 months, without the occurrence of early ScT and without usage of (new) oral anticoagulants ((N)OAC).

Ethics

This is an observational study, performed based on international regulations, including the declaration of Helsinki. Data were collected in an encrypted database with the approval of the local ethics committee. The Absorb BVS received the CE mark and the BVS can be currently used routinely in Europe in different settings without a specific written informed.

Procedure

PCI was performed according to current clinical practice standards. The radial or femoral approach using 6 or 7 French catheters were the principal route of vascular access. All patients were treated with unfractionated heparin (at a dose of 70-100 UI/ kg). According to the guidelines, patients with stable angina were preloaded with 300 mg of aspirin and 600 mg of clopidogrel. Patients presenting with ACS were preloaded with 300 mg of aspirin and 60 mg of prasugrel or 180 mg of ticagrelor. Previous guidelines for DES and per hospital policies were used to prescribe DAPT and this was also based on the operator's instructions.

Follow-up

Survival status was obtained from municipal civil registries. Follow-up information specific for hospitalization and major cardiovascular events was obtained through questionnaires that were mailed individual patients at 1, 6, 12 and 18 months after procedure. In case of an absent response after reminder mail, patients were called thereafter or information was gathered from general practitioners or hospitals. Information on DAPT status and the stopping date of P2Y12 inhibitor were collected. When an exact stopping date was available (through questionnaires, pharmacies, general practitioners or hospital letters), the date was used to compute the duration of DAPT. When patients did not exactly recall the precise stopping date but instead noted that he or she used DAPT for a period of one year, duration of DAPT was recorded as 365 days. In case of a patient writing that he/ she had visited the hospital, aditional medical records and discharge letters were consulted to check if any event had occurred.

Definitions

ScT was classified as ST according to the Academic Research Consortium (ARC). [16] ScT were reported reported as either acute (≤24 hours), subacute (1-30 days), late (30-365 days) and very late (>365 days). DAPT termination was described as the date on which one of the two components of DAPT (aspirin or P2Y12 inhibitor) had been terminated.

Endpoints

The primary endpoint in the DAPT study cohort was the incidence rate of definite or probable ScT beyond 6 months while the patient was either using DAPT or had terminated DAPT. This time period (6 – 18 months) was chosen because we assumed that, based on the healing process, the pathophysiology of scaffold thrombosis in the period between 6 and 18 months was similar. To investigate the time relation with DAPT more in detail, an additional analysis was performed for the first month after DAPT termination compared to the incidence rate while on DAPT.

Statistical analysis

Categorical variables are reported as counts and percentages, continuous variables as mean ± standard deviation or median (25^{th}-75^{th} percentile). For each time period, the ScT incidence was calculated as the number of events divided by the sum of the follow-up times for each individual. The variable 'on DAPT' was computed as the stopping date of DAPT minus the date of the index procedure. In case of a ScT while the patient was using DAPT, 'on DAPT' was reported as days until the event. 'Off DAPT' was calculated as 18 months post-procedure (or the latest available follow-up date) minus the time period until termination of the P2Y12 inhibitor. In case of ScT while DAPT was terminated, days off DAPT were computed as follows: date of ScT minus date of DAPT termination. The cumulative incidence of study endpoints was estimated according to the Kaplan-Meier method. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical tests were patient-based, two-sided and the P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 21 (IL, US).

RESULTS

Between September 2012 and January 2015, 808 patients were included in the pooled database. The DAPT study cohort consisted of 685 patients (figure 1). Survival status in this group was known in 100% and median follow-up duration was 730 (interquartile range [IQR]: 531.8 – 923.3) days. Median duration of DAPT was 367 (IQR: 365 – 398) days and with a range from 180 to 1237 days. Hundred and thirty (19%) had a DAPT duration

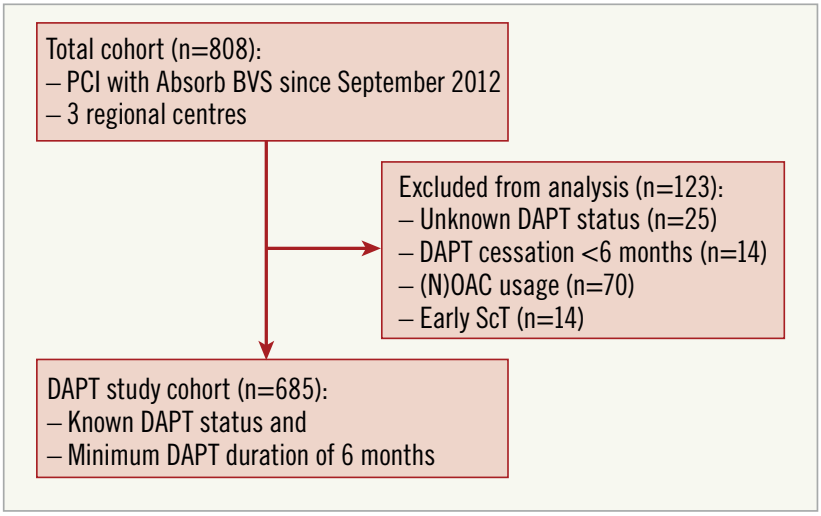

Figure 1 Study flow chart

ranging between 6 months and 1 year and 81% had a DAPT duration of at least 365 days. Eighty-nine patients (12.9%) continued DAPT until the last follow-up. Figure 3A displays the individual duration of DAPT for the patients.

Baseline characteristics

Baseline characteristics of both the full cohort and the DAPT study cohort are presented in table 1. In the DAPT study cohort, mean age was 57.9 (±10.6) years, 73.9% were male, 14.3% were diabetic, and 12.4 % had a history of myocardial infarction. Most patients (70.3%) presented with ACS. The largest part of the patients used a more potent P2Y12 inhibitor such as prasugrel or ticagrelor (76.6%). Mean number of lesions/ patients was 1.19 (±0.45). Moderate or severe lesion calcification, as assessed by angiography, was present in 32.9% and bifurcation in 21.3%. AHA/ ACC lesion classification type B2/ C was present in 45.7%.

Procedural details

Procedural details are described in table 2. In the DAPT study cohort, a total of 964 BVS were implanted. Pre-dilatation was performed in 88.3% of the patients, post-dilatation in 56.7 % and intravascular imaging (OCT or IVUS) in 31.3%. A 2.5 mm BVS was used in 21.8%. Mean scaffold diameter and mean scaffold length were 3.1 (± 0.4) mm 20.9 (± 5.8) mm. Device success and procedural success were achieved in 98.3% and 98.0%, respectively.

Table 1. Patient and lesion characteristics

	Total cohort N=808, L=949	DAPT study cohort N=685, L=813
Median follow-up in days (IQR)	729 (516 – 899.75)	730 (531.8 – 923.3)
Gender (%)		
Men	73.9	73.9
Women	26.1	26.1
Mean age in years (±SD)	58.46 (10.91)	57.9 (10.6)
Smoking (%)	50.8	51.5
Hypertension (%)	47.9	45.0
Dyslipidemia (%)	45.9	45.4
Diabetes Mellitus (%)	14.2	14.3
Family history of CAD (%)	48.8	49.5
Prior MI (%)	12.8	12.4
Prior PCI/ CABG (%)	13.7	13.4
Presentation with multivessel disease (%)	30.8	30.3
Indication for PCI (%)		
Stable angina	26.6	26.1
Unstable angina	10.1	10.0
NSTEMI	30.7	31.2
STEMI	28.6	29.1
Silent ischemia	3.9	3.6
Periphery artery disease (%)	3.8	3.2
Heart failure (%)	4.0	2.5
Renal insufficiency (%)	3.3	2.5
ASA + P2Y12 inhibitor (%)		
clopidogrel	39.8	38.3
prasugrel	38.2	38.3
ticagrelor	22.0	23.4
Median duration of DAPT in days (IQR)		367 (365 – 398)
Min and max DAPT duration in days		180 - 1237
Number of lesions per patient (±SD)	1.17 (0.44)	1.19 (0.45)
Left anterior descending artery (%)	54.4	54.2
Left circumflex artery (%)	20.9	21.4
Right coronary artery (%)	24.7	24.4
Bifurcation (%)	23.0	21.3
Calcification (moderate or severe) (%)	33.7	32.9
CTO (%)	3.1	3.2

Table 1. Patient and lesion characteristics (*continued*)

	Total cohort N=808, L=949	DAPT study cohort N=685, L=813
ACC/ AHA lesion classification (%)		
A	10.3	10.3
B1	43.5	44.0
B2	28.4	27.3
C	17.8	18.4

ASA: Aspirin; CABG: coronary artery bypass grafting ; CAD: coronary artery disease; CTO: chronic total occlusion; DAPT: dual antiplatelet therapy; IQR: interquartile range; L:lesions; MI: myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; P: patients; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction

Table 2. Procedural characteristics

		Total cohort P=808, L=949	DAPT study cohort P=685, L=813
Pre-dilatation (%)		88.4	88.3
Invasive imaging at baseline (%)		30.8	31.3
Total number of scaffolds implanted		1119	964
	2.5 mm BVS (%)	22.7	21.8
	3.0 mm BVS (%)	39.2	40.7
	3.5 mm BVS (%)	38.1	37.4
Mean scaffold diameter, mm (±SD)		3.08 (0.38)	3.08 (0.38)
Mean scaffold length, mm (±SD)		20.90 (5.83)	20.94 (5.83)
Mean total scaffold length per patient, mm (±SD)		32.48 (20.99)	33.14 (21.60)
Overlap (%)		29.7	30.6
Post-dilatation (%)		55.4	56.7
Clinical device success (%)		98.0	98.3
Clinical procedure success (%)		97.2	98.0

Clinical outcomes

In the total cohort of 808 patients, 26 definite or probable ScT occurred with a cumulative event rate, described as Kaplan-Meier estimate, of 3.3% (95% CI: 2.1 – 4.5) at 18 months (figure 2). The majority (1.7%) were early ScT: acute ScT rate was 0.2% (95% CI: -0.2 – 0.6) and subacute ScT rate was 1.5% (95% CI: 0.7 – 2.3). Late and very late ScT were less frequent: 1.0% (95% CI: 0.2 – 2.0) and 0.6% (95% CI: 0.02 – 1.2) respectively. In the DAPT study cohort Kaplan-Meier estimates for late and very late ScT were similar (0.9% and 0.7% respectively).

Figure 3B shows the duration in days while off DAPT and the association with very late ScT in the DAPT study cohort. Four cases of very late definite/ probable ScT occurred: at 379 days (10 days after DAPT termination), at 416 days (35 days after DAPT termina-

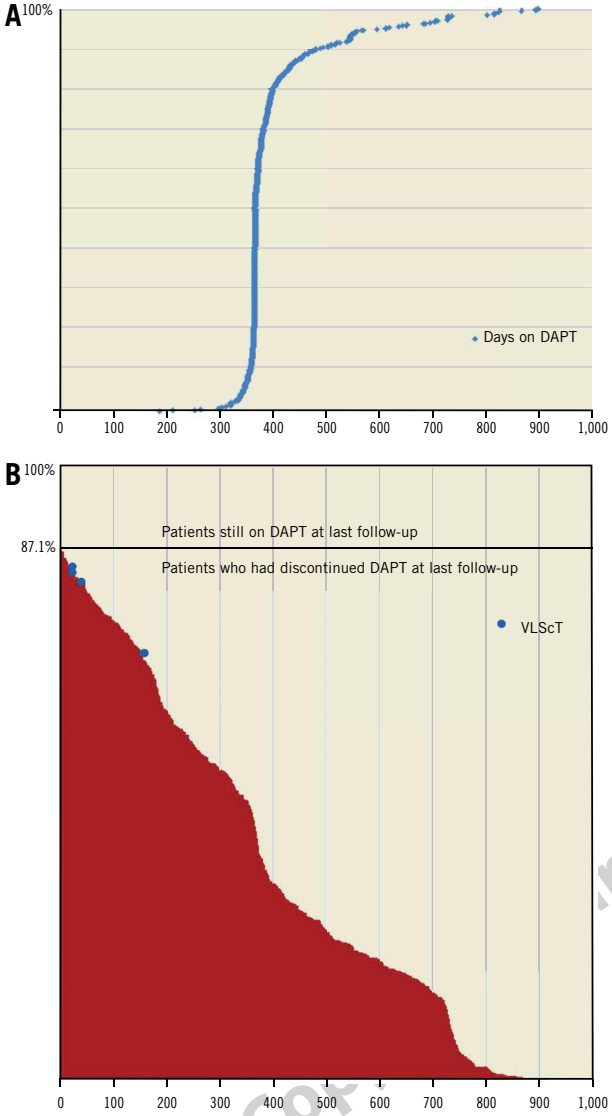

Figure 2 DAPT duration for all individual patients
A) Days on DAPT in the DAPT study cohort. B) Days off DAPT in the DAPT study cohort. Blue dots indicate the ScT timing in relation to the number of days off DAPT. VLScT: very late scaffold thrombosis.

tion) at 429 days (20 days after DAPT termination) and 526 (149 after DAPT termination). Cases have been described elsewhere. [17] These four patients were using aspirin but had terminated P2Y12 inhibitor. Their duration of DAPT was a little over 365 days. However, this was not based on a specific reason such as an increased ischemic risk. Rate of definite/ probable ScT in this particular time frame was 0.7%.

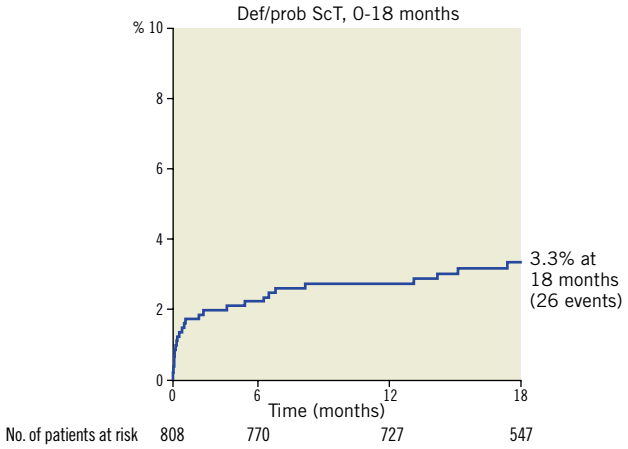

Figure 3 Cumulative ScT rate in the total cohort from the index procedure up to 18 months post procedure.
ScT: scaffold thrombosis

For reasons of comparability with current literature, incidences per 100 patient-years (py) were computed in the DAPT study cohort (figure 4, table 3). For calculating the incidence of ScT in the time period 6 - 18 months, 607.52 py were available and 5 events occurred (one late ScT and 4 very late ScT) with an incidence of 0.83/ 100 py (95% CI: 0.34 – 1.98).

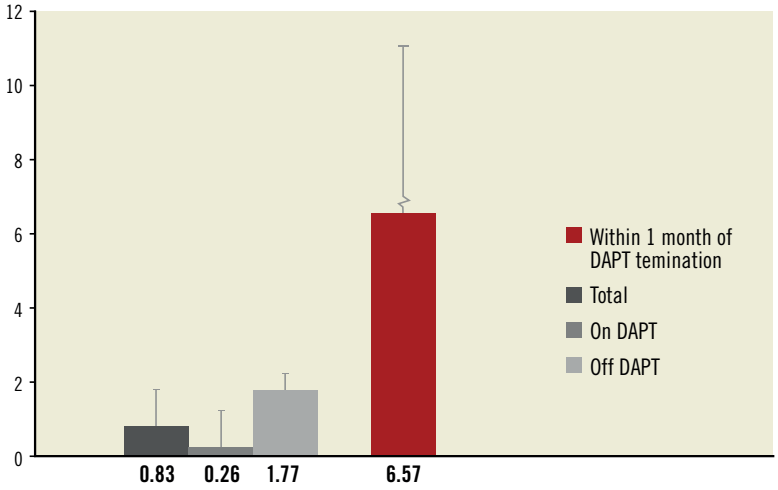

Figure 4 Incidence densities for the whole DAPT study cohort, in patients on and off DAPT and within the first month of termination in the DAPT study cohort.
DAPT: dual antiplatelet therapy.

Table 3. Incidences of definite/ probable ScT per 100 patient-years

	Incidence rates per 100 patient-years (95% CI) 6 – 18 months
Total	0.83 (0.34 - 1.98)
On DAPT period	0.26 (0.04 – 1.86)
Off DAPT period	1.77 (0.66 – 4.72)
Within 1 month of DAPT termination	6.57 (2.12 – 20.38)

DAPT: dual antiplatelet therapy; py: patient-years; ScT: scaffold thrombosis

For the period on DAPT, 381.90 py were available and 1 event occurred (at day 208). This resulted in an incidence of 0.26/ 100 py (95% CI: 0.04 – 1.86). For the period after DAPT termination, 225.62 py and 4 events were reported with ScT incidence of 1.77/ 100 py (95% CI: 0.66 – 4.72), numerically 6.8 times higher than the incidence on DAPT but not statistically significant (p=0.12).

For the incidence of ScT in the first month of DAPT termination, 45.64 py were available and 3 events occurred, which subsequently provided an incidence of 6.57/ 100 py (95% CI: 2.12 – 20.38). This was statistically significant when compared to the incidence in the on DAPT period (p=0.01). The incidence of ScT during the last month of DAPT usage was 0.

DISCUSSION

To our knowledge this is the first study that reports on the impact of DAPT termination on the occurrence of definite/ probable ScT in Absorb BVS in a clearly defined study cohort, reflecting real-world patients. The main findings of our study are as follows: 1) Incidence of definite or probable late and very late ScT in patients that are on DAPT is low; 2) All cases of very late ScT at 18 months were not using DAPT at time of the event; 3) Incidence of ScT in patients off DAPT is potentially increased within the first 18 months post-implantation, with the highest incidence within one month after termination of DAPT.

Overall incidence of late and very late ScT

Overall, late and very late scaffold thrombosis rate in this multi-center, real-world registry was acceptable and comparable to the rates in selected populations as included in approval studies for different countries. [11, 12, 15] In this study and regardless of DAPT status, the overall incidence density of late and very late def/ prob ScT were 1.0 and 1.44 per 100 patient-years respectively. A large all-comer observational cohort study, investigating ST in metal DES during 4-year follow-up, reported a late ST incidence density of

0.4 def/ prob ST per 100 patient-years in patients treated with newer-generation EES. For SES and PES, incidence densities were higher for both late (SES: 0.7/ 100 patient-years and PES: 1.5 per 100 patient-years) and very late ST (SES: 2.8/ 100 patient-years and PES: 4.0/ 100 patient-years). In this regard, late and very late ScT incidence in BVS patients seems comparable to first generation metal DES.[18]

DAPT and late events

At 18 months, there were 4 patients with VLScT, all while not using DAPT during the event. Three out of four cases appeared to be associated with DAPT termination. The incidence density was 1.79/ 100 patient-years in patients who were not continually on DAPT. Importantly, incidence of ScT within one month of DAPT termination was even higher. In the Absorb Extend study, 50% of the ScT cases were related to either premature DAPT termination or resistance to clopidogrel. [19] The ABSORB Japan trial reported two years follow-up. Two out of four patients with VLScT were not using DAPT at time of the event. In the recently published ABSORB II RCT , three-year results revealed 6 cases of VLScT. Of note, all cases of late and very late ScT occurred in patients off DAPT. Moreover, in patients who did not terminate DAPT up to 3 years, no ScT were described. [12] In our series, the relationship between the moment of DAPT termination and occurrence of VLScT was notable, with 3 out of 4 cases within 35 days of DAPT termination, a finding not so clear in the ABSORB II and ABSORB Japan trials. Thus, as reported in multiple studies, DAPT termination seems to play an important role in the occurrence of VLScT.

Possible causes late ScT

Other factors besides DAPT termination, that were associated with ScT were suboptimal implantation technique, late discontinuities, uncovered struts, neoatherosclerosis, high maximum footprint, small minimal lumen diameter, small vessels, higher % diameter stenosis, overlap, ostial lesions and decreased LVEF. [11, 20-25] Late and very late ScT while DAPT was terminated, might be explained by the high volume of implanted material with special attention the increased strut thickness, which could cause laminar flow disturbance and subsequently the triggering of platelet deposition. [26] This might be a special problem in small vessels or when full dilatation was not achieved without high pressure post-dilatation using non-compliant balloons. In early BVS-registries, there was a higher risk of malapposition, often induced by undersizing, which occurs regularly. [5] During the first large studies in BVS patients, high pressure post-dilatation with non-compliant balloons was not mandatory as result of a case where strut fractures were observed. Nowadays, a different implantation tactic for BVS is used after an optimal implantation strategy, started in January 2014, was associated with a large reduction in ScT incidence. [20, 27] Also, thinner strut BVS are currently being developed, which will mitigate the risk of ScT.

STUDY LIMITATIONS

This was a retrospective and registry data – pooled study. As the sample size is limited and numbers of this low-frequence event are small, these results should be interpreted with caution and considered hypothesis generating. More data and dedicated studies are needed to confirm our suggestion to prolong DAPT in BVS treated patients. Lastly, quantitative coronary analysis (QCA) was not available in all patients.

CONCLUSION

The incidence of probable/ definite late and very late ScT in BVS patients who are on DAPT in our study is low. However, the incidence of early ScT and also the occurrence of very late ScT are not negligible. Between 6 and 18 months, incidence of ScT in patients who terminated DAPT is potentially increased.

Impact on daily practice

As long as studies with an optimal implantation strategy haven't revealed data on safe DAPT termination before 18 months, it would be reasonable to consider extension of DAPT. Prolonging DAPT even up to three years could be a possible solution in patients with an increased risk of ischemic events and low bleeding risk (the DAPT score can be used for risk assessment [28]), as the resorption process of Absorb BVS is completed in 3 years and until that time, the polymer is still present and the risk of very late ScT is lurking. The decision whether or not to continue DAPT beyond a certain time point cannot be made by a 'one size fits all' principle and should be individual-based.

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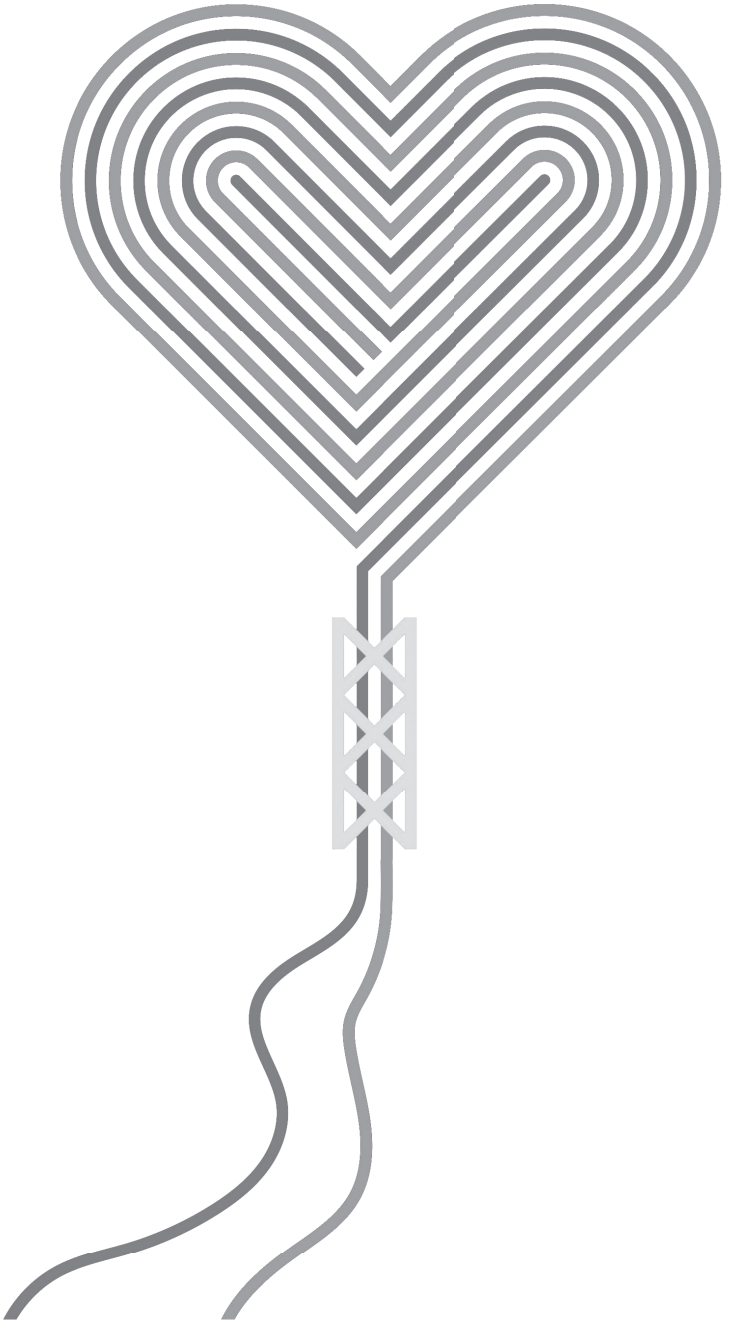

Epilogue

Chapter 15

Mid-term outcomes of the BVS versus second generation DES: a systematic review and meta-analysis

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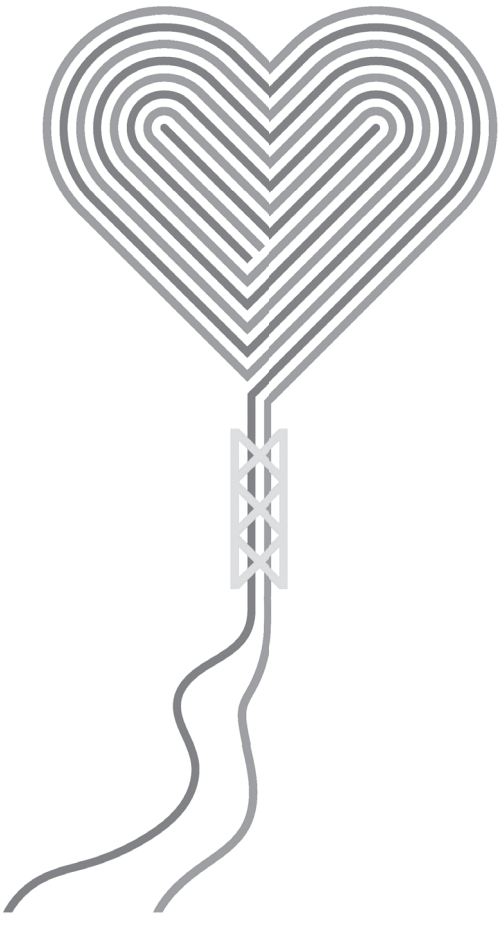

ABSTRACT

Background

Bioresorbable Vascular Scaffolds (BVS) were introduced to overcome some of the limitations of drug-eluting stent (DES) for PCI. Data regarding the clinical outcomes of the BVS versus DES beyond 2 years are emerging.

Objective

To study mid-term outcomes.

Methods

We searched online databases (PubMed/Medline, Embase, CENTRAL), several websites, meeting presentations and scientific session abstracts until August 8th, 2017 for studies comparing Absorb BVS with second-generation DES. The primary outcome was target lesion failure (TLF). Secondary outcomes were all-cause mortality, myocardial infarction, target lesion revascularization (TLR) and definite/probable device thrombosis. Odds ratios (ORs) with 95% confidence intervals (CIs) were derived using a random effects model.

Results

Ten studies, seven randomized controlled trials and three propensity-matched observational studies, with a total of 7320 patients (BVS n=4007; DES n=3313) and a median follow-up duration of 30.5 months, were included. Risk of TLF was increased for BVS-treated patients (OR 1.34 [95% CI: 1.12-1.60], p=0.001, I^2=0%). This was also the case for all myocardial infarction (1.58 [95% CI: 1.27-1.96], p<0.001, I^2=0%), TLR (1.48 [95% CI: 1.19-1.85], p<0.001, I^2=0%) and definite/probable device thrombosis (of 2.82 (95% CI: 1.86-3.89], p<0.001 and I^2=40.3%). This did not result in a difference in all-cause mortality (0.78 [95% CI: 0.58-1.04], p=0.09, I^2=0%). OR for very late (>1 year) device thrombosis was 6.10 [95% CI: 1.40-26.65], p=0.02).

Conclusion

At mid-term follow-up, BVS was associated with an increased risk of TLF, MI, TLR and definite/probable device thrombosis, but this did not result in an increased risk of all-cause mortality.

CONDENSED ABSTRACT

Pooled 1-year results of RCTs in selected patients showed non-inferiority of target lesion failure (TLF) for bioresorbable vascular scaffolds (BVS). Meta-analyses that included more complex patients revealed an increased risk for TLF and scaffold thrombosis in BVS-treated patients. This meta-analysis reports on mid-term outcomes from 10 studies comparing Absorb BVS versus second-generation drug-eluting stents. At a weighted median FU of 30.5 months, risks of TLF, all myocardial infarction, target lesion revascularization and definite/probable device thrombosis were increased in BVS-treated patients, which did not result in higher all-cause mortality.

INTRODUCTION

Bioresorbable scaffolds, developed to overcome some of the (late) adverse events of metallic drug-eluting stents (DES), are the latest innovation in the treatment of coronary artery disease. The Absorb bioresorbable vascular scaffold (BVS, Abbott Vascular, Santa Clara, CA, USA) is the most intensively studied. The first-in-man study in 2006 revealed promising results and this new device received a CE-mark in 2011 and became commercially available in Europe in September 2012. FDA approval followed in 2016 [1].

The concept of the Absorb BVS consists of treatment of obstructive coronary artery disease with temporary support of the vessel wall while avoiding the acute complications of balloon angioplasty. It was hypothesized that complete resorption would result in restoration of vasomotion, a reduction in angina, and the avoidance of caging of the vessels or interference with non-invasive imaging. In addition, vessel geometry would be less affected after implantation of a BVS. This should result in better outcomes for patients, with reduced late event rates. Pooled individual data from the four largest randomized controlled trials (RCTs) comparing BVS with second-generation DES did support the concept of temporary support of the artery and showed non-inferiority of the device during the first year [2]. However, several meta-analyses that included data beyond 1 year revealed higher event rates of myocardial infarction, target lesion revascularization and scaffold thrombosis [3, 4]. Data on the performance of BVS beyond 1 year primarily came from small registries, propensity-matched observational studies and a few RCTs. These raised concerns about the occurrence of very late (after 1 year) scaffold thrombosis [5], whereas RCTs assessed only the mid-term time points. We therefore undertook this systematic review and meta-analysis, and report the mid-term clinical outcomes of the Absorb BVS compared with second-generation DES.

METHODS

Data sources and study selection

Inclusion criteria for our study were RCTs comparing the Absorb BVS with the Xience CoCr-EES, a second-generation DES, in patients with coronary artery disease with > 12 months of follow-up available. As randomized mid- to long-term data are scarce, we also allowed propensity-matched observational studies comparing BVS with second-generation DES. Both full-length manuscripts and meeting presentations (containing unpublished data) were included. All studies had to report on the outcomes of interest and be written in English. Exclusion criteria were non-human studies, single-arm studies, imaging-only studies, studies with short follow-up (≤ 12 months), studies in <100 patients, review articles, case series, trial design articles, comparisons other than Absorb BVS versus second-generation DES, studies with duplicate data, and those where the scaffold or stent was implanted elsewhere than in the coronary artery. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [6] (S4 Table).

Data extraction and quality assessment

On August 8th , 2017, a medical librarian (WB) conducted a systematic search of the online databases Medline/PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL), several websites (e.g. www.clinicaltrials.gov) and scientific session abstracts and oral presentations from conferences, with the following keywords and corresponding MeSH terms: "drug-eluting stent(s)", "everolimus-eluting stent", "bioresorbable vascular stent", "bioresorbable scaffold". On October 31th, during the 2017 TCT congress, ABSORB II, III and TROFI II presented their 3- and 4-year outcomes, which we also included in our analysis. The bibliographic records retrieved were imported and de-duplicated in Endnote bibliographic software. Two physician reviewers (CF and VB) independently screened the records for eligibility at title or abstract level. Records that were relevant were downloaded and full text manuscripts or meeting presentations were reviewed. Differences between reviewers regarding study selection or data extraction were resolved by consensus. If one study had multiple publications with different follow-up lengths, the most recent follow-up record was used.

Quality and risk of bias in reporting data were assessed according to the Cochrane Handbook of Systematic Reviews [7] and by using the Newcastle-Ottawa Quality Assessment scale for case-control studies (maximum score = 9, meaning low risk of bias). Publication bias for the primary endpoint was assessed using funnel plot.

Outcomes and definitions

The primary outcome for this analysis was target lesion failure (TLF), a composite endpoint that consists of cardiac death, target-vessel myocardial infarction and ischemia-driven TLR. Secondary outcomes were all-cause mortality, all myocardial infarction, ischemia-driven TLR and definite or probable device thrombosis. Deaths were considered cardiac unless a non-cardiac cause was identified. TLR was described as any repeated revascularization of the target lesion. Device thrombosis was classified according to the Academic Research Consortium [8]. To investigate the effect of the intended bioresorption of the device, we examined outcomes during the first and second years separately. Definitions of clinical outcomes per study are described in S1 Table.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were used as summary statistics across all studies and were calculated using a random effects model (Dersimonian and Laird). We also provide results of the fixed-effect model. Treatment effect was not assessed in studies in which no events were reported. Heterogeneity was assessed using Cochran Q and Higgins I^2. I^2 values of <25%, 25-50% or >50% indicate low, moderate or high heterogeneity. Cochran Q P<0.10 and I^2>50% were considered to be indicative of significant heterogeneity. All analyses were conducted with Revman software (version 5.3).

Primary and secondary outcomes are reported for all included studies in which the outcome of interest was provided. A sensitivity analysis was performed, as detailed in the online supplement. In this analysis, the treatment effect was investigated in studies that included low-risk patients (ABSORB II, ABSORB III, ABSORB Japan, ABSORB China) versus studies that included more complex population (TROFI II, AIDA, EVERBIO and the observational studies, including higher percentage of STEMI, bifurcation, calcification, long lesions etc.). Finally, separate subgroup analyses for RCTs (low risk of bias) and propensity-matched studies (low/low-moderate risk of bias) were performed.

The risks of adverse events between 0 – 1 year, 1 – 2 and 2 -3 years were estimated using a landmark population that censored any casualty and lost to follow-up preceding each specific time point.

Trial sequential analysis

Meta-analyses may results in type 1 errors due to systematic errors (several forms of bias) or random errors (play of chance) due to sparse data and repeated significance testing when a meta-analysis is updated with new trials [9]. This can result in spurious significant results [10]. Trial sequential analysis (TSA) was introduced to minimize random errors. TSA provides the necessary information for meta-analyses and boundaries that determine whether the evidence is reliable and conclusive. We calculated required information size allowing for a type 1 error of 0.05, type 2 error of 0.20, the control event

proportions and effect size calculated from the included trials, and heterogeneity estimated by the diversity (D2) in the included trials. We constructed TSA boundaries based on the O'Brien-Fleming alpha-spending function. Trial Sequence Analysis Software (Copenhagen Trial Unit's TSA Software; Copenhagen, Sweden) was used.

RESULTS

The de-duplicated results yielded 1305 records. Figure 1 shows a flow diagram of the selection process. Based on the exclusion criteria, 1278 records were excluded after title/abstract review. Twenty-seven records remained for full-text analysis, of which 17 were eliminated (short follow-up or editorials). Ultimately, we included 7 RCTs (3 full-length

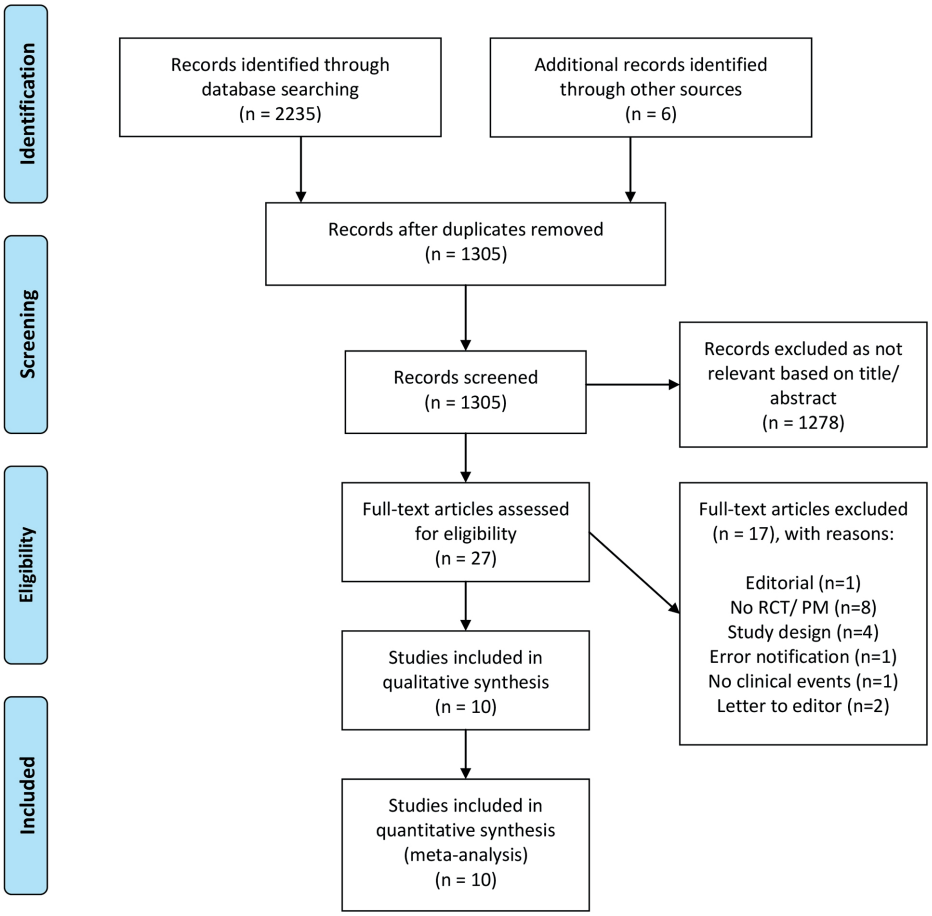

Figure 1 Flowchart

manuscripts, 4 meeting presentations) with a total of 5578 patients: 3258 received the Absorb BVS and 2320 received a second-generation DES. We also included 3 observational studies (2 manuscripts and 1 meeting presentation) with 1742 patients: 749 were implanted with a BVS and 993 with a DES. Weighted median FU was 30.5 months. Table 1 summarizes the main characteristics of the included studies.

Table 1. Major characteristics of included studies

Study	Year	Centres, n	BVS/ DES treated Patients, n	Study type	Clinical presentation	Primary Endpoint	Follow-up, yrs.
ABSORB II [28]	2016	46	335/ 166	RCT	SAP, established ACS	Vasomotion & LLL (at 3 yrs.)	1, 2, 3, 4
ABSORB III [27]	2017	193	1322/ 686	RCT	SAP, established ACS	TLF (at 1 yr.)	1, 2, 3
ABSORB Japan [36]	2016	38	266/ 134	RCT	SAP, established ACS	TLF (at 1 yr.)	1, 2, 3
ABSORB China [37]	2016	24	238/ 237	RCT	SAP, established ACS	LLL (at 1 yr.)	1, 2, 3
TROFI II [26]	2016	8	95/ 96	RCT	STEMI	HS (at 6 months)	1, 2, 3
EVERBIO [38]	2017	1	78/ 80	RCT	SAP, ACS, silent ischemia	LLL (at 9 months)	9 months, 2 yrs.
AIDA [39]	2017	5	924/ 921	RCT	SAP, ACS	TVF (at 2 yrs.)	Median of 707 days
Imori et al. [40]	2016	8	214/ 215	Propensity matched	ACS	MACE	2
BVS-Examination [41]	2016	6	290/ 290	Propensity matched	STEMI	POCE (at 1 yr.)	1, 2
BVS Expand [42]	2017	1	244/ 488	Propensity matched	SAP, UA, NSTEMI, silent ischemia	MACE	2

ACS: acute coronary syndrome; DOCE: device oriented composite endpoint; HS: healing score; LLL: late lumen loss; MACE: major adverse cardiac events; RCT: randomized controlled trial; SAP: stable angina pectoris; STEMI: ST-elevation myocardial infarction; TLF: target lesion failure; LLL: late lumen loss; TVF: target vessel failure; UAP: unstable angina pectoris

Baseline characteristics

Across all studies in this meta-analysis, the mean age of patients ranged from 56.0 to 67.3 years; the percentage of men between 70.1% and 81.4%; diabetic patients between 12.8% and 36.1%; and the percentage of patients that presented with an acute coronary syndrome between 9.8% and 100%. In all studies except ABSORB II and EVERBIO, the per protocol prescribed duration of dual antiplatelet therapy (DAPT) was at least 12 months. The percentage of BVS patients using DAPT at 2 years ranged from 5.5% to 66%. The rate of post-dilatation ranged from 15.2% to 82.2% (Table 2).

Table 2. Baseline characteristics (presented as BVS versus EES)

	ABSORB II	ABSORB III	ABSORB Japan	Absorb China	TROFI II	EVERBIO	AIDA	Imori et al.	BVS-Examination	BVS Expand
Patients										
Randomized, n	355/ 166	1322/ 686	266/ 134	238/ 237	95/ 96	78/ 80	924/ 921	214/ 215	290/ 290	244/ 488
Age, years	61.5/ 60.9	63.5/ 63.6	67.1/ 67.3	57.2/ 57.6	59.1/ 58.2	65/ 65	64.3/ 64.0	59.7/ 61.5	56.0/ 57.6	61.3/ 61.9
Male sex (%)	76/ 80	70.7/ 70.1	78.9/ 73.9	71.8/ 72.6	76.8/ 87.5	80/ 78	72.5/ 76.0	79.4/ 80.5	81.4/ 79.7	73.4/ 73.6
Diabetes (%)	24/ 24	31.5/ 32.7	36.1/ 35.8	25.2/ 23.2	18.9/ 14.7	16/ 22	18.5/ 16.6	14/ 16.7	12.8/ 12.8	18.4/ 20.7
Hypertension (%)	69/ 72	84.9/ 85.0	78.2/ 79.9	58.8/ 60.3	44.1/ 36.5	64/ 55	50.9/ 50.5	56.1/ 54.4	49.7/ 43.8	60.1/ 63.7
Dyslipidaemia (%)	75/ 80	86.2/ 86.3	82/ 81.1	42.4/38.4	63.8/ 57.3	63/ 64	37.6/ 38.3	41.1/ 42.8	41.7/ 45.5	50.6/ 54.7
ACS at presentation (%)	23/ 25	26.9/ 24.5	9.8/ 16.4	72.3/ 75.9	100/ 100 (only STEMI)	34/ 37	53.6/ 54.6	100/100	100/100 (only STEMI)	59.1/ NA
Previous MI (%)	28.0/ 29.0	21.5/ 22.0	16/ 23.9	16.8/ 16.0	2.1/ 3.1	18/ 14	18/ 18.7	NA	3.5/ 3.5	17.2/ 18.1
Previous PCI (%)	12.0/ 9.0	NA	3.4/ 5.2	9.7/8.0	4.2/ 3.1	31/ 32	21.9/ 20.0	NA	3.4/ 3.8	9.4/ 15.2
DAPT per protocol	At least 6 months	At least 1 year	At least 1 year	At least 1 year	At least 1 year	At least 6 months	At least 1 year	1 year	1 year	1 year
On DAPT at 2 yrs. (%)	36.2/ 34.3	66/ 65.6	52.3/ 50.7	NA	NA	21/ 15	17.5/ 15.6	NA	5.8/ 17.0	5.7/ NA
Lesions										
Randomized, n	364/ 182	1385/ 713	275/ 137	251/252	95/ 98	112/ 96	1237/ 1209	NA	NA	355/ NA
ACC/ AHA B2/C (%)	46/ 49	68.7/ 72.5	76/ 75.9	74.9/ 72.1	NA	35/ 29	55.0/ 51.0	48/42 (C)	NA	38.1/ NA
Calcification (moderate/ severe, %)	13/ 15.5	NA	34.6/ 43.7	17.5/15.5	NA	NA	30.0/ 28.0	NA	NA	42.2/ NA
Bifurcation (%)	0/ 0	0/ 0	0/ 0	50.2/ 48.6	NA	NA	5.0/6.0	NA	NA	21.3/ NA
Lesion length (mm)	13.8/ 13.8	12.6/ 13.1	13.5/ 13.3	14.1/ 13.9	12.88/ 13.41	NA	19.1/ 18.8	NA	NA	22.10/ NA
Pre-procedural RVD (mm)	2.6/ 2.6	2.67/ 2.65	2.72/ 2.79	2.81/ 2.82	2.86/ 2.76	2.77/ 2.39	2.67/ NA	NA	NA	2.42/ NA
Pre-procedural DS (%)	59/ 60	65.3/ 65.9	64.6/ 64.7	65.3/ 64.5	89.5/ 89.9	NA	NA	NA	NA	59.13/ NA
Pre-dilatation (%)	100/ 99	100/ 100	100/ 100	99.6/ 98.0	55.8/ 51.0	97/ 86	97.0/ 91.0	NA	81.0/ 29.0	89.8/ NA
Intravascular imaging (%)	100/ 100	11.2/ 10.8	68.8/ 68.7	0.4/ 0.4	NA	NA	NA	23/ NA	NA	39.0/ NA
Post-dilatation (%)	61/ 59	65.5/ 51.2	82.2/ 77.4	63.0/ 54.4	50.5/ 25.5	31/ 34	74.0/ 49.0	55.2/ NA	36.3/ 15.2	53.3/ NA
Maximum pressure (atm)	14.2/ 15.0	15.4/ 15.4	14.7/ 15.1	16.8/ 16.9	15.8/ 18.6	13.6/ 14.6	15.4/ 15.6	20/ NA	NA/ NA	15.5/ NA
In-device MLD (mm)	2.22/ 2.50	2.37/ 2.49	2.42/ 2.64	2.48/ 2.59	2.46/ 2.46	2.56/ 2.62	NA	NA	NA	2.30/ NA
Post-procedural DS (%)	16/ 10	11.6/ 6.4	11.8/ 7.1	12.2/ 8.7	14.1/ 13.4	9.3/ 8.1	17.0/ NR	NA	NA	16.90/ NA

Values are presented as means or percentages and are described as BVS/ DES. ACS: acute coronary syndrome; DAPT: dual antiplatelet therapy; DS: diameter stenosis; MLD: minimum lumen diameter; NA: not available; RVD: reference vessel diameter.

Clinical outcomes

All studies but one (BVS Expand) reported on TLF. Overall, TLF occurred in 617 patients during the mid-term follow-up, with a significantly higher risk in BVS-treated patients (OR 1.34 [95% CI: 1.12-1.60], p=0.001 and I^2=0%) (Figure 3A). A subanalysis of RCTs showed only a significantly similar increased OR (1.31 [95% CI: 1.08-1.58], p=0.005 and I^2=0%). The pooled OR across the observational studies was numerically higher, but with a larger 95% CI (OR 1.57 [95% CI: 0.92-2.68, p=0.10, I^2=0%). In the TSA for the primary endpoint, the cumulative Z-curve did cross the TSA monitoring boundary, indicating that there were a sufficient number of patients to consider this a valid analysis (Figure 2A). See S2 and S8 Figures for the sensitivity analyses and S3-S7 Figures for fixed effects models of the primary and secondary outcomes.

Secondary endpoints

All-cause mortality occurred in 207 patients, without a statistically significant difference between both patient groups (OR 0.78 [95% CI: 0.56-1.37], p=0.09, I^2=0%). Results for the pooled RCT and pooled observational study subgroups were similar (Figure 3B).

The risks of myocardial infarction and TLR were significantly increased for BVS compared with DES (Figures 3C and 3D). Finally, patients with BVS had a higher risk for definite or probable device thrombosis, with ORs of 2.82 (95% CI: 1.86-3.89], p<0.001 and I^2=40.3%), 3.48 (95% CI: 2.06-5.87, p<0.001 and I^2=0%) and 2.82 (95% CI: 1.86-4.26, p<0.001 and I^2=0%), respectively, for the total cohort, RCTs only and observational data only (Figure 3E).

Landmark analysis

Table 3 summarizes event rates and ORs in the periods up to 1 year, 1-2 years and 2-3 years (for those studies that reported 1- and 2-year and 3-year results of the outcomes of interest: ABSORB II, ABSORB Japan, ABSORB China, ABSORB III). In the first year, the risks of myocardial infarction and device thrombosis were significantly increased in BVS patients. During the second year, all event rates for both BVS and DES were lower, but the increased risk for BVS remained. The OR for late device thrombosis was quadrupled in BVS-treated patients. In the third year, events rates remained lower and no significant differences between the 2 groups existed anymore. However, the OR for device thrombosis in BVS patients continued to be high.

Definite/ probable device thrombosis

For the secondary endpoint definite or probable device thrombosis, we specifically investigated early (0-30 days), late (31 days-1 year) and very late (> 1 year) device thrombosis (for studies that reported the outcome of interest at these three time points). Event rates for early thrombosis were 1.07% for BVS versus 0.51% for DES. This resulted in an

increased risk for BVS (OR 1.96 [95% CI: 1.01-3.81], p=0.05). Late device thrombosis event rates were 0.53% for BVS versus 0.09% for DES (OR 3.14 [95% CI: 0.83-11.82, p=0.09). Rates of very late device thrombosis up to three years were 1.09% for BVS compared to 0.0% for DES (OR 6.10 [95% CI: 1.40-26.65], p=0.02).

The sensitivity analysis results can be found in S2 Figure.

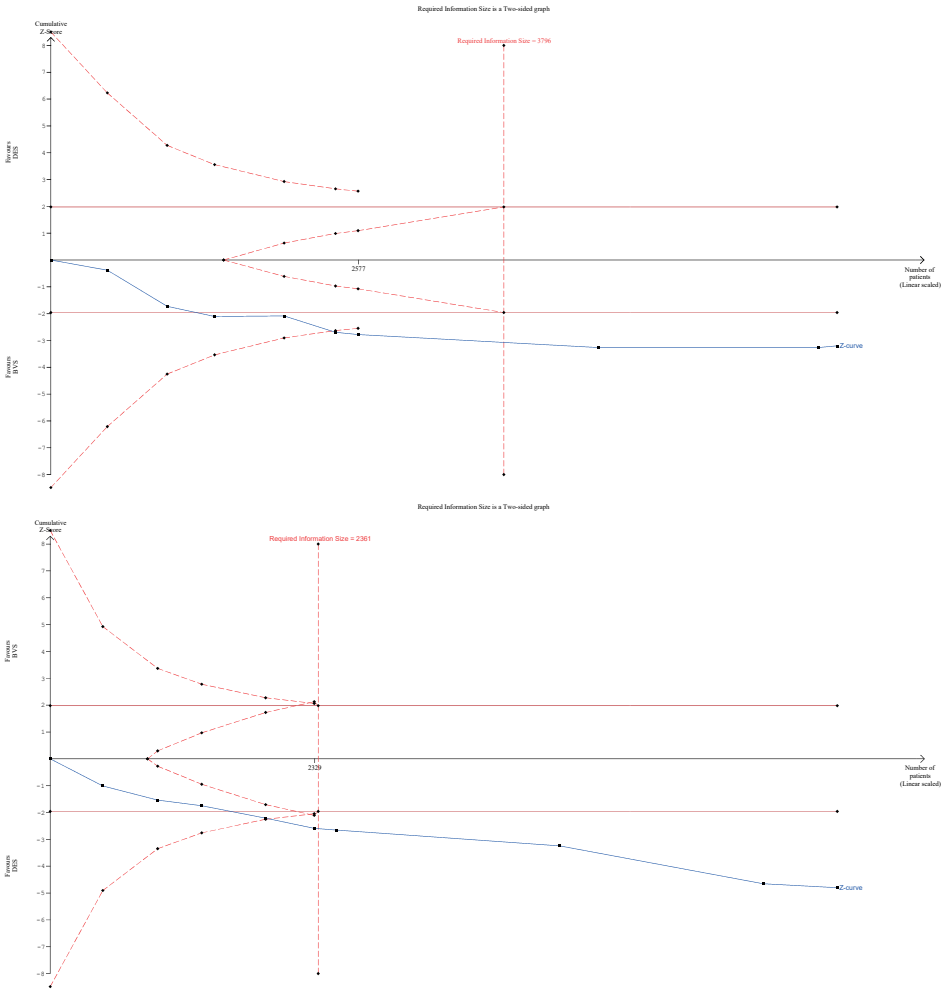

Figure 2 Trial Sequential Analysis for (A) Primary Endpoint Target Lesion Failure and Definite/Probable Device Thrombosis (B)

The red dotted line represents the trial sequential monitoring boundaries and the futility boundaries. The solid dark red line illustrates the conventional level of significance (p=0.05). The cumulative Z score (solid blue line) crosses both the conventional boundary and the trial sequential monitoring boundary, indicating sufficient and conclusive evidence.

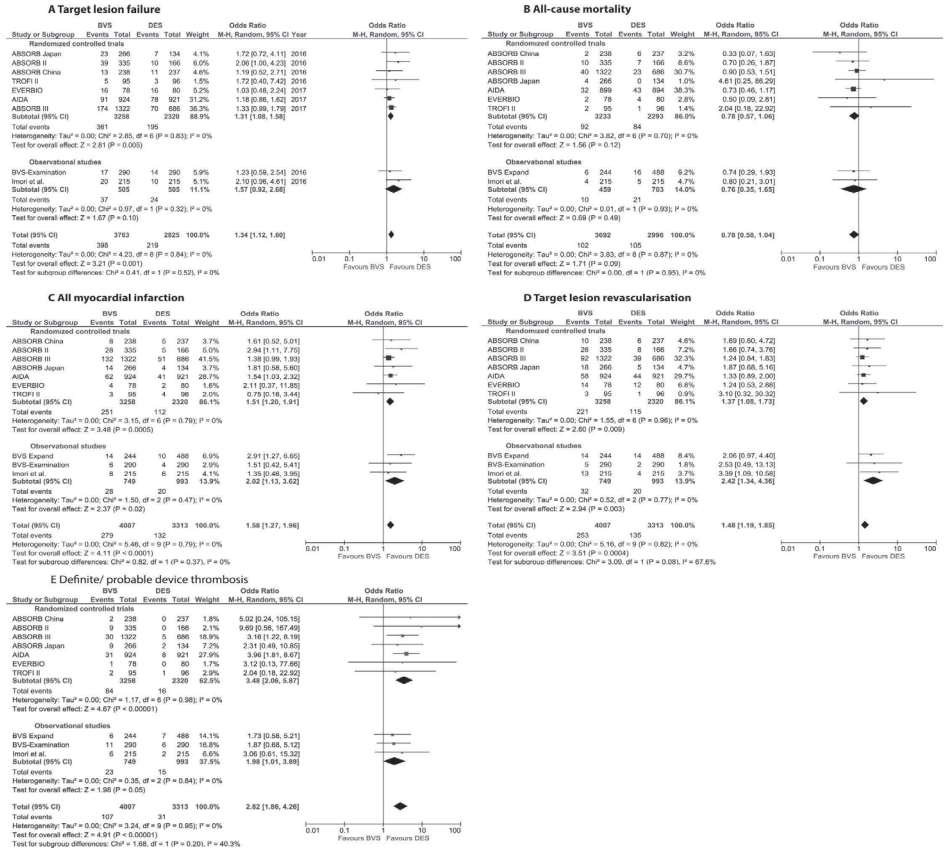

Fig 3. 3A ± 3E. Forest plots (random effects models) for primary and secondary endpoint of bioresorbable vascular scaffolds versus drug-eluting stents. (A) Target lesion failure, (B) All-cause mortality, (C) All myocardial infarction, (D) Target lesion revascularization. RCTs reported ischemia-driven TLR and observational studies reported all TLR. (E) Definite/ probable device thrombosis. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.

Quality assessment

Quality assessments for both RCTs and observational studies are provided in the S2 and S3 Tables. All RCTs had a low risk of bias, while the observational studies had a low/ low-moderate risk of bias (all scored 7 out of 9). To assess a possible publication bias, a funnel plot for TLF was derived (S1 Figure).

DISCUSSION

This study included 7320 patients, to report on the mid-term clinical outcomes of the Absorb BVS compared with second-generation DES. Compared to other meta-analyses

[11-14], our analysis included the RCTs and complemented only with propensity matched registries to include the highest quality data available for more complex patients. Using this strategy we were able to perform a sub analysis for RCT and propensity match series representing the more complex none RCT patients and a separate analysis for 2 to 3 year outcomes. Furthermore, a trial sequential; analysis was performed and also, several

Table 3. Outcomes of interest at 0 -1 year, 1 -2 years and 2 -3 years (for included studies that presented outcomes at these time points*)

Outcome	Up to 1 year				1 -2 years				2 – 3 years			
	BVS	DES	OR (95% CI)	P	BVS	DES	OR (95% CI)	P	BVS	DES	OR (95% CI)	P
TLF (%)	6.39	5.15	1.24 (0.97 – 1.58)	0.09	4.43	2.55	1.55 (0.98 – 2.46)	0.06	1.20	0.34	2.75 (0.97 - 7.78)	0.06
All-cause mortality (%)	1.17	1.49	0.90 (0.33 – 2.43)	0.83	1.10	1.73	0.65 (0.4 – 1.05)	0.08	0.20	1.88	0.14 (0.01 – 1.46)	0.10
Myocardial infarction (%)	5.15	3.50	1.38 (1.04 – 1.83)	0.03	2.20	1.01	2.17 (1.30 - 3.62)	0.003	1.36	0.94	1.18 (0.59 - 2.37)	0.64
ID-TLR (%)	3.08	2.57	1.26 (0.90 – 1.77)	0.18	2.87	1.59	1.67 (0.97 – 2.87)	0.06	2.11	1.02	1.79 (0.62 – 5.15)	0.28
Def/ prob device thrombosis (%)	1.60	0.61	2.45 (1.35 – 4.46)	0.03	0.86	0.10	4.75 (1.63 – 13.82)	0.004	0.53	0.00	3.79 (0.67 – 21.37)	0.13

*ABSORB II, ABSORB III, ABSORB China, ABSORB Japan. Def/ prob: definite/probable; OR: Odds ratio; ID-TLR: ischemia driven target lesion revascularization; TLF: target lesion failure

sensitivity analyses were done such an analysis of more complex patients versus non-complex patients.

The main findings of this meta-analysis are: 1) BVS-treated patients were at higher risk for TLF, MI, TLR and device thrombosis compared with second-generation DES, across all studies included in this meta-analysis; 2) this did not result in an increased risk of all-cause mortality; 3) based on studies that have reported clinical outcomes of interest at 1, 2 and 3 years of follow-up, risks of TLF, MI, TLR and especially the risk of very late device thrombosis, continued to be higher for BVS in following years after device implantation.

In our study, propensity matched registries were included. There are some advantages of registries over clinical trials. Firstly, registries handle less strict in- and exclusion criteria and therefore create a more 'real-world' patient population [15]. Results originating from registries are better generalizable. Secondly, registries often make use of longer-term follow-up then duration of follow-up observed in RCTs. Thirdly, the larger amount of events makes the identification of rare events, such as ScT, possible. Fourth, as registries integrate data less selected patients, receiving care in diverse clinical settings, they are able to better investigate specific subgroups that are often underrepresented in clinical trials.

Initial study designs for BVS, based on the concept of temporary vascular support, hypothesized non-inferiority at one year and a reduction in TLF of approximately 50% beyond the first year. In this analysis, we demonstrated that event rates were highest during the first year after PCI and, for all endpoints except all-cause mortality; the use of BVS was associated with significantly higher risks of events. The mid-term results in this meta-analysis are in line with previous results [12, 16-21]. Beyond 1 year, event rates were lower than during the first year, but outcomes such as device thrombosis, myocardial infarction and the primary endpoint – TLF – remained not in favour of BVS.

Four RCT's reported their three-year results and one RCT presented four-year results. All revealed continued higher event rates for BVS. During the EuroPCR 2017 congress, longer term data of several large single-arm registries, that included higher percentages of complex patients, was presented and with varying results [22].

Definite/ probable device thrombosis

In our study, we demonstrated that the risk of definite device thrombosis was almost three times higher for BVS. Meta-analyses investigating device thrombosis in BVS compared with DES have reported an increased risk of device thrombosis for BVS [5, 23, 24]. Multiple factors have been reported to be associated with scaffold thrombosis, such as a suboptimal implantation strategy, overlap, ostial lesions and decreased left ventricular ejection fraction [25]. Moreover, the first-generation BVS has a strut thickness considerably larger than the competitor metallic DES and similar to first-generation metallic DES. Scaffold thrombosis might be triggered by the smaller minimum lumen diameter and minimum lumen area at the end of the procedure, as previously demonstrated [26]. This has the most impact on smaller vessels (with a diameter <2.5 mm visual or 2.25 mm by quantitative coronary analysis (QCA).

Early device thrombosis is generally considered to be procedure-related, when the characteristics of the device and operators experience are important factors.

The resorption process of the BVS might influence the mechanisms for very late scaffold thrombosis. It has been postulated that the disintegration of uncovered and malapposed struts (due to resorption-related scaffold discontinuity) might trigger the inflammatory process and thrombus formation, potentially for up to 3 years (18, 26, 27).

Recent setback

Recently, the ABSORB BVS suffered a setback after the 3-year results of the ABSORB II trial demonstrated similar vasomotion between BVS and everolimus-eluting DES and a greater late lumen loss for BVS. [27, 28] The FDA came with a safety alert after the 2-year results of the largest RCT, the ABSORB III, were presented during the ACC congress in March 2017. The AIDA trial even published their 2-year results earlier than expected after the safety monitoring board recommended to release the preliminary data due to

safety concerns (hazard ratio of 3.87 for device thrombosis at 2 years; 95% CI: 1.78 – 8.42; p=<0.001). As a consequence, the current generation BVS has been taken out of the market. Just recently, a Task Force of ESC and EAPCI stated that bioresorbable scaffolds should not be preferred above the current used metallic DES [29]. These unfavourable findings were again confirmed during the 2017 TCT congress in Denver, USA on October the 31th. [30-32]

Possible solutions and future outlook

It remains uncertain whether implantation technique could improve outcomes. The basic concept of optimal implantation includes proper lesion preparation, adequate sizing (avoiding small vessels <2.5 mm) and high-pressure post-dilatation, also known as PSP. In retrospective analyses, this implantation strategy showed a reduction in TLF [25] [22, 33-35]. Also, the 30-day ABSORB IV results revealed lower device thrombosis rates, when implantation of stents/ scaffolds in small vessels was minimalized. [36] The prospective study 'IT-DIAPPEARS' showed that when a predefined implantation technique was performed, one-year outcomes were favourable with a def/ prob ScT rate of 0.9%. [37] However, our meta-analysis was not able to correctly assess the influence of PSP on procedural and clinical outcomes, as the included studies did not apply high rates of dedicated implantation strategy.

Furthermore, whether DAPT prolongation could prevent late occurrence of scaffold thrombosis was to be investigated. DAPT termination is a risk factor for device thrombosis, and a possible relationship between scaffold thrombosis and DAPT termination has been described. However, information on the precise duration of DAPT after BVS implantation is lacking and, up to this moment, no dedicated studies exist on this important issue. A recently published review has suggested several considerations for DAPT duration in BVS patients [38]. In metal stents, prolongation of DAPT up to 30 months showed to reduce thrombotic events [39]. The new generation device should have thinner struts, better mechanical properties and shorter resorption time to facilitate easy implantation strategies and to prevent intraluminal dismantling [40].

LIMITATIONS

The most important limitation is the use of unpublished data in the form of meeting presentations. Secondly, the meta-analysis was performed using study-level data rather than patient-level data, so time-to-event curves were not possible. Thirdly, heterogeneity existed in baseline characteristics of included patients and also in protocols, study designs and definitions across the studies. Furthermore, the patients included in the RCTs (which provided most patients) were highly selected (except for AIDA) and, there-

fore, extrapolation to the real world is difficult. Besides, we were not able to completely exclude potential confounders in the observational registries. However these studies were based on propensity matching. Fourthly, the large AIDA RCT had a median follow-up duration of 1.93 years (range 1–3.3 years); thus this trial did not report outcomes at exactly 2 years.

Longer follow-up will be necessary to get a better view of the low-frequency endpoint mortality.

To assess possible publication bias, we provided a funnel plot in S1 Figure. However, this plot should be interpreted with caution as we included ten studies. There was also a lack of important information on DAPT status (duration of DAPT, reasons for interruption or early termination, type of $P2Y_{12}$ inhibitor). Lastly, the current data only apply for the Absorb BVS and not for other bioresorbable devices.

CONCLUSIONS

At mid-term follow-up, patients treated with Absorb BVS showed a higher risk of TLF, myocardial infarction, TLR and definite or probable device thrombosis. Beyond 1 year, it was mainly the risk of late device thrombosis that was increased. However, this did not result in a higher risk of all-cause mortality. Despite these unfavourable mid-term outcomes, long-term follow-up will be necessary to investigate any potential late benefits of BVS over DES as this device was not able to show any clinical benefit up to 3 years. Specific registries and post-hoc analyses of larger RCTs identified potential improvements in patient and lesion selection. A device specific implantation strategy is another factor that can result in better outcomes. As long as this has not been demonstrated in prospective and dedicated studies such as ABSORB III (NCT01751906), ABSORB IV (NCT02173379) and Compare Absorb (NCT02486068) operators should not use this version in routine practice.

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SUPPLEMENTAL MATERIAL

Table 1A. Definitions of Clinical Outcomes Per Study (A) RCTs and (B) registries

	ABSORB II	ABSORB III	ABSORB Japan	ABSORB China	TROFI II	EVERBIO II	AIDA
Target lesion failure	Cardiac death, target-vessel MI, ID-TLR	Cardiac death, target-vessel MI, ID-TLR	Cardiac death, target-vessel MI, ID-TLR	Cardiac death, target-vessel MI, ID-TLR	Cardiac death, MI (not clearly attributable to a non-target vessel), ID-TLR	Cardiac death, target-vessel MI, CD-TLR	Cardiac death, target-vessel MI, CD-TLR
Device thrombosis	ARC definitions	ARC definitions	ARC definitions	ARC definitions	ARC definitions	ARC definitions	ARC definitions
Myocardial infarction	New pathological Q-wave or CK rise > 2 of ULN accomplice by CK-MB rise	*Periprocedural:* CK-MB to >5x ULN within 48 hours in cases in which the baseline CK-MB value is <ULN *Spontaneous:* defined as elevation of troponin >ULN or CK-MB >ULN and ≥ of the following: ischemic symptoms, ischemic ECG changes, development of pathological Q waves, or imaging findings of acute MI	*Periprocedural:* CK-MB >5x ULN. *Spontaneous:* Troponin>ULN or CK-MB>ULN and ≥ of the following: ischemic symptoms, ischemic ECG changes, development of pathological Q waves, or imaging findings of acute MI	*Periprocedural:* CK-MB >5× ULN *Spontaneous:* defined as elevation of troponin >ULN or CK-MB >ULN and ≥ of the following: ischemic symptoms, ischemic ECG changes, development of pathological Q waves, or imaging findings of acute MI	New pathological Q-waves in ≥ 2 contiguous leads (as assessed by the ECG core laboratory) with or without post-procedure troponin, CK or CK-MB levels elevated above normal; Detection of a rise and/ or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99 percentile ULN and ≥ of the following: ischemic symptoms, ischemic ECG changes, development of pathological Q waves, or imaging/ autopsy findings of acute MI	*Periprocedural:* According to Global MI Task Force for the Universal definition of Myocardial Infarction [35] *Spontaneous::* Development of new pathological Q waves ≥0.04 s in duration in ≥2 contiguous leads or an elevation of creatine phosphokinase levels to >2 times normal with positive creatine phosphokinase–MB or troponin I levels	'Third Universal Myocardial infarction' definitions[35]

Table 1A. Definitions of Clinical Outcomes Per Study (A) RCTs and (B) registries (*continued*)

	ABSORB II	ABSORB III	ABSORB Japan	ABSORB China	TROFI II	EVERBIO II	AIDA
Target lesion revascularization	Any clinically indicated repeat PCI of the target lesion or CABG of the target vessel	Any repeat PCI of the target lesion or CABG of the target vessel	Any repeat PCI of the target lesion or CABG of the target vessel	Any repeat PCI of the target lesion or CABG of the target vessel	Any repeat PCI of the target lesion or CABG of the target vessel	Repeat revascularization within the stent or the 5-mm boarders proximal and distal to the stent.	Any repeat PCI of the target lesion or CABG of the target vessel
Death	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established	All deaths were considered cardiac unless an unequivocal non-cardiac cause was established

CABG: coronary artery bypass grafting; CK: creatine kinase; CK-MB: creatine kinase myoglobulin; ID-TLR: ischemia-driven target lesion revascularization; MI: myocardial infarction, ULN: upper limit of normal

Table 1B.

	BVS-Examination	Imori et al.	BVS Expand
Target lesion failure	Cardiac death, target-vessel MI, TLR	NA	Cardiac death, target-vessel MI, ID-TLR
Patient oriented endpoint	All-cause death, any MI, any revascularization	NA	NA
Device thrombosis	ARC definitions	ARC definitions	ARC definitions
Myocardial infarction	Based on Historical Extended Definition of MI (modified ARC Definition according to Vranckx *et al*. [33])	NR	Based on Historical Extended Definition of MI (modified ARC Definition according to Vranckx *et al*. [33]) and per protocol definition of MI also known as the World Health Organization Definition of MI.

ID-TLR: ischemia-driven target lesion revascularization; MI: myocardial infarction; NA: not applicable; ULN: upper limit of normal

Table 2. Assessment of Risk of Bias for Randomized Controlled Trials

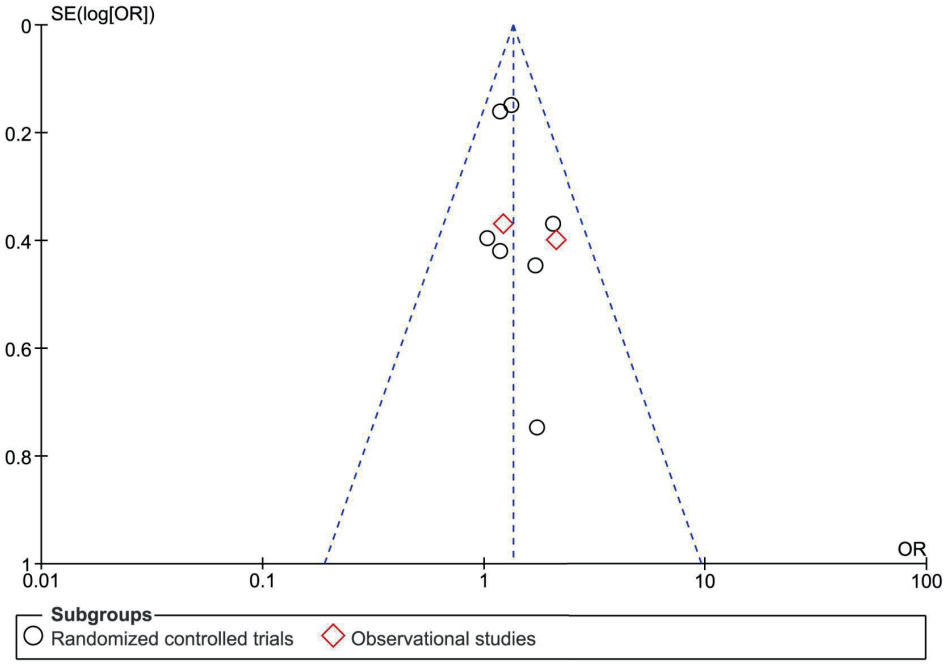
Trial	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Sample size calculation	Sponsor
ABSORB II	IWRS	Yes	Yes	Yes (independent CEC)	Yes	No	Yes	Industry
ABSORB III	IWRS	Yes	Yes	Yes (independent CEC)	Yes	No	Yes	Industry
ABSORB Japan	IWRS	Yes	Yes	Yes (independent CEC)	Yes	No	Yes	Industry
ABSORB China	IWRS	Yes	No	Yes (independent CEC)	Yes	No	Yes	Industry
AIDA	IWRS	Yes	Yes	Yes (independent CEC)	Yes	No	Yes	Investigator
TROFI II	IWRS	Yes	No	Yes (independent CEC)	Yes	No	Yes	Investigator
EVERBIO II	IWRS	Yes	Yes	Yes (independent CEC)	Yes	No	Yes	Investigator

CEC: clinical event committee; IWRS: interactive web-based response system

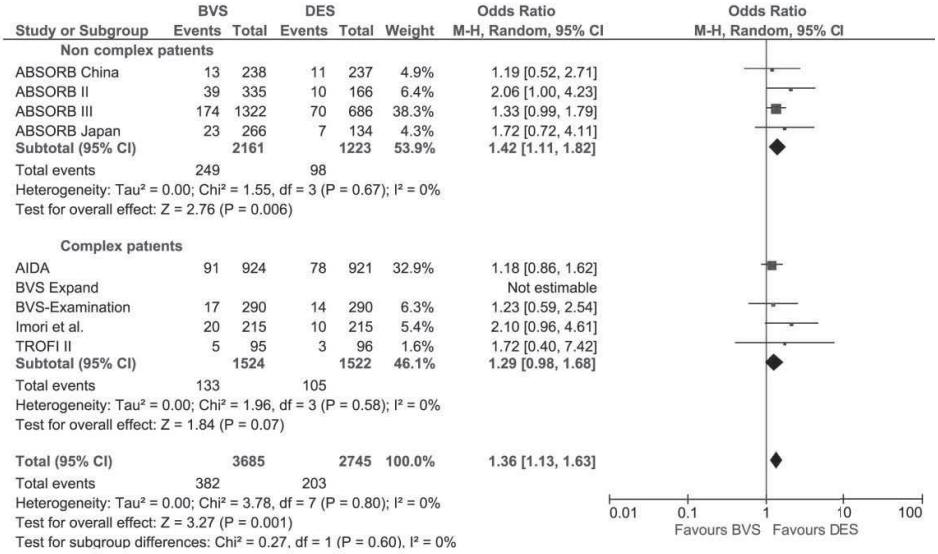
Table S3. Quality assessment for observational studies

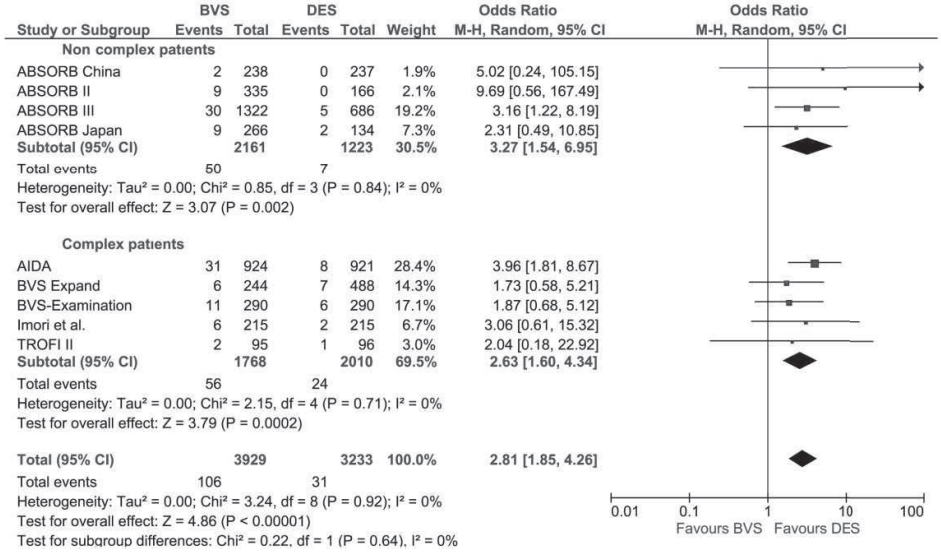
Study	Selection	Comparability on basis of design and analysis	Outcome
Imori et al.	****	*	***
BVS Examination	****	*	***
BVS Expand	****	*	***

Score of nine is maximum score (= lowest risk of bias)

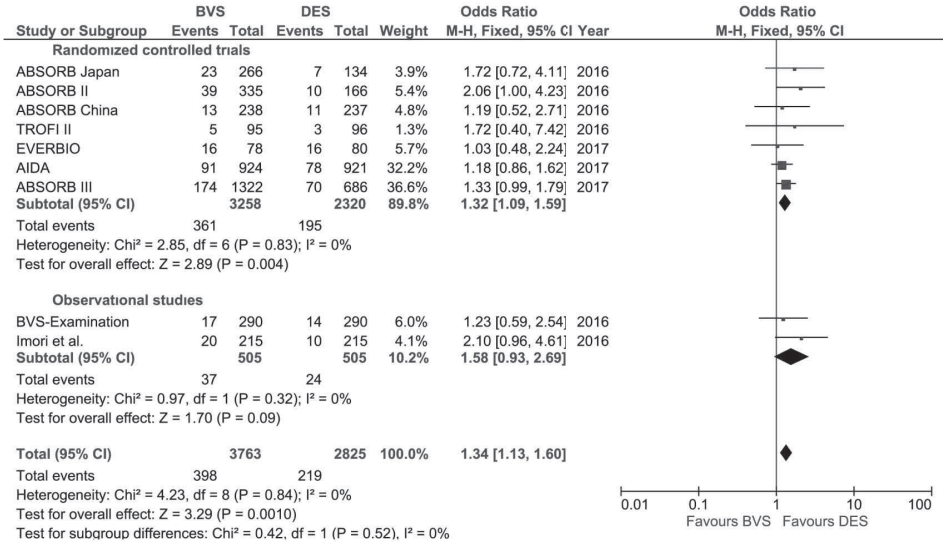


S1 Fig. Funnel Plot for the Primary Endpoint



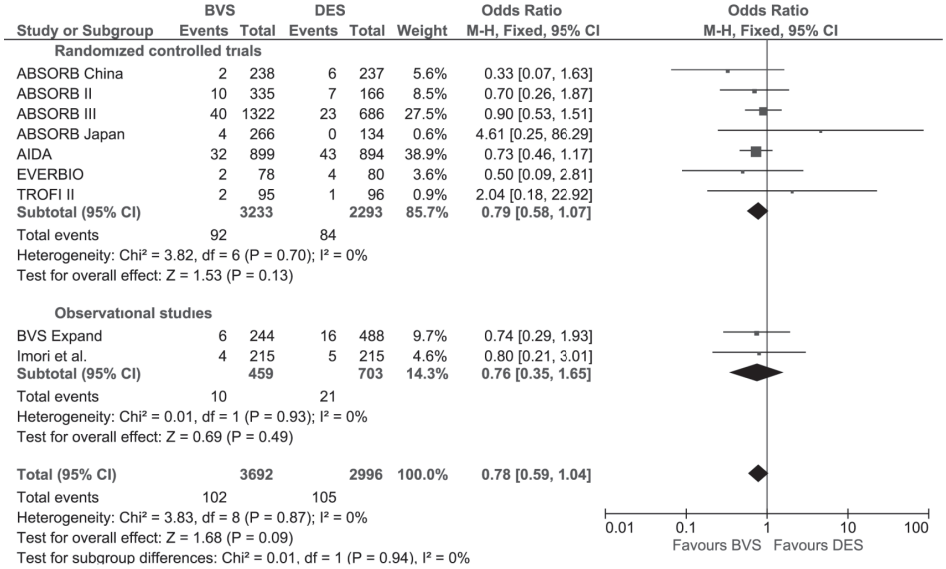


S2 Fig. Sensitivity analysis for TLF and device thrombosis. Non-Complex Studies Versus Complex Studies. Random effects effects model. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.



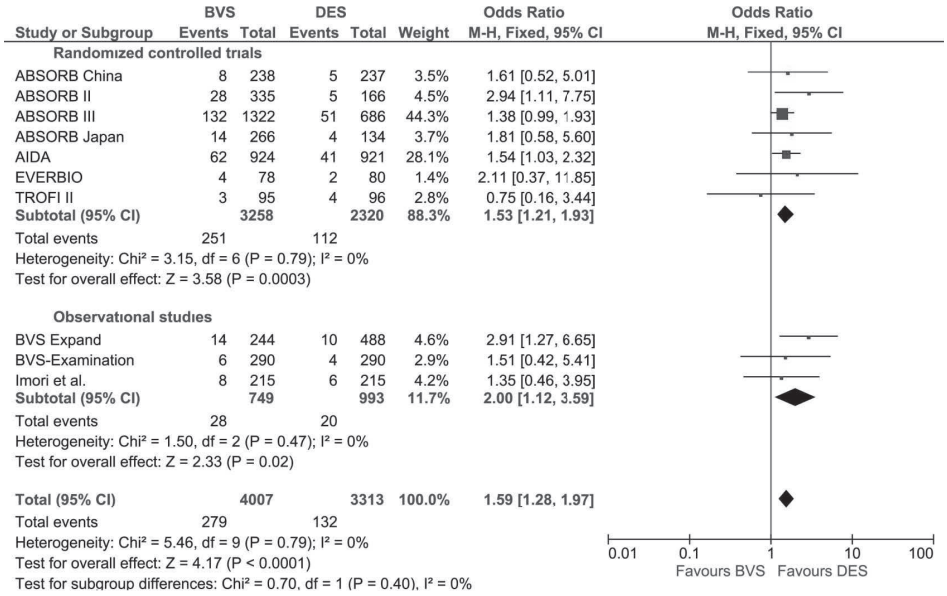
S3 Fig. Target lesion failure.

Fixed effects model. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.



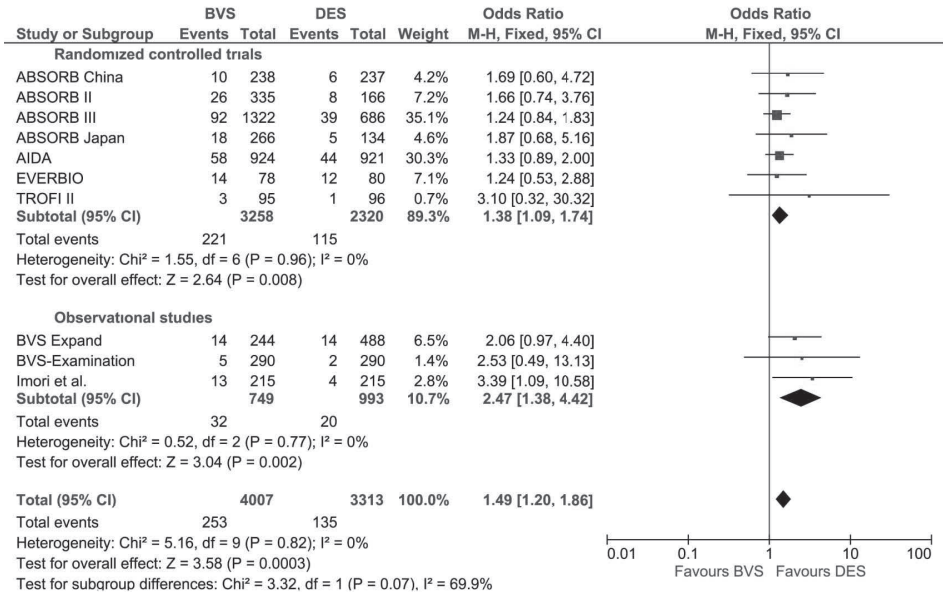
S4 Fig. All-cause mortality.

Fixed effects model. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.



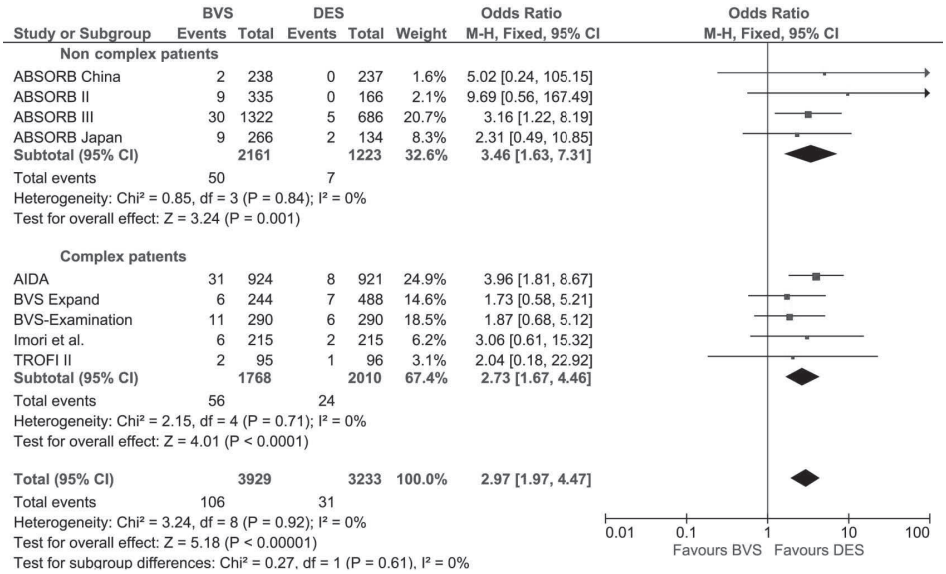
S5 Fig. Myocardial infarction.

Fixed effects model. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.



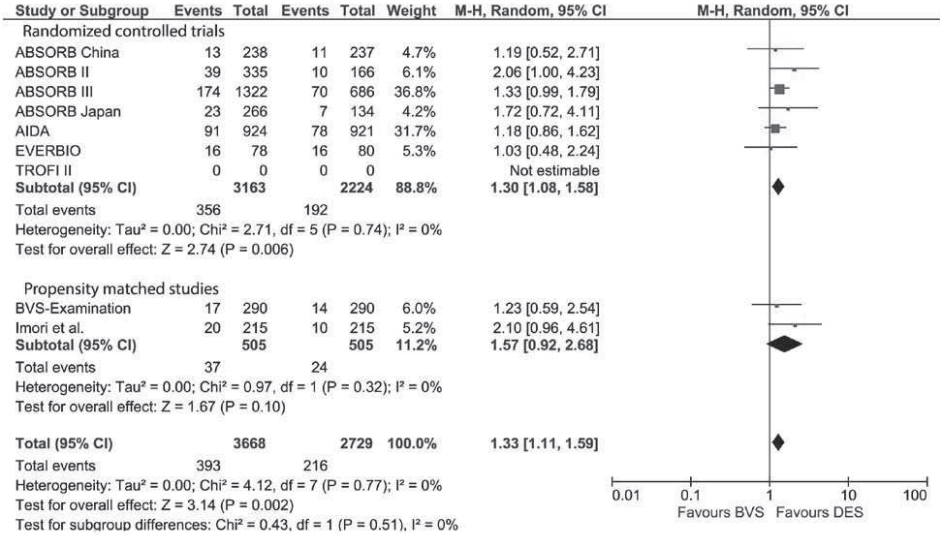
S6 Fig. Target lesion revascularization.

Fixed effects model. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.



S7 Fig. Definite/Probable device thrombosis.
Fixed effects model. CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.

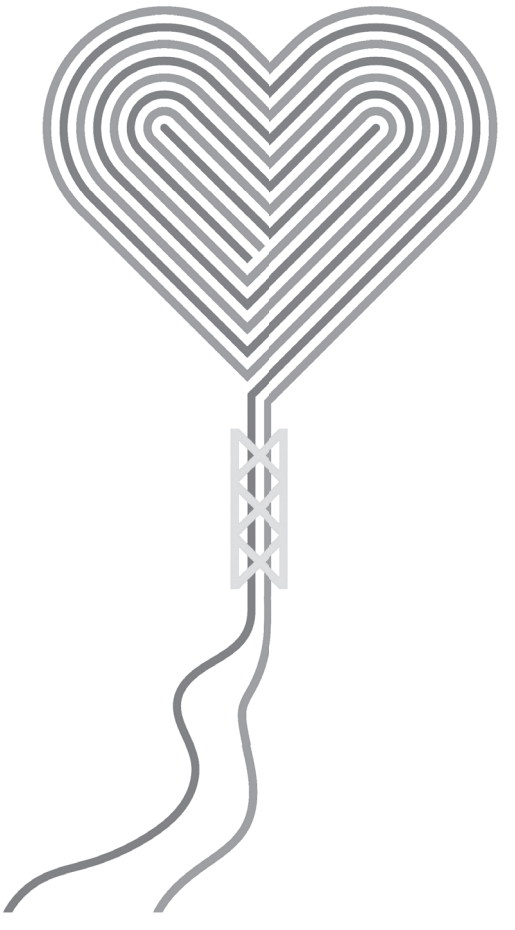
S8 Figure Sensitivity analysis for TLF, RCTs versus propensity matched studies



S8 Fig. Sensitivity analysis for TLF. RCTs versus propensity matched studies. Randomeffects effects model. Caption: CI: confidence interval; M-H: Mantel-Haenszel; OR: odds ratio.

Chapter 16

Summary



Drug-eluting stents (DES) are widely used as first choice devices in percutaneous coronary interventions (PCI). However, certain concerns are associated with the use of DES, i.e. neo-atherosclerosis, late stent thrombosis and hypersensitivity reactions to the DES polymer. Bioresorbable scaffolds (BRS) such as the Absorb Bioresorbable Vascular Scaffold (BVS) are the next development within the field of PCI, introducing the concept of supporting the natural healing process following initial intervention without leaving any foreign body materials resulting in late adverse events. The first-generation devices have shown encouraging results in multiple studies of selected patients with non-complex lesions up to the point of full bioresorption. It supported the introduction in regular patient care. During its introduction in daily clinical practice outside the previous selected patient groups, a careful approach should be followed in which outcome is continuously monitored. The aim of this thesis was to investigate the safety and efficacy of the Absorb BVS in more complex lesions and higher-risk patients, when treated in a diverse clinical practice.

In Chapter 1, an overview was provided of available studies during that time point (2014/ 2015), demonstrating encouraging results in selected patients and with limited duration of follow-up. Together with a group of early expert users, we set up a Dutch consensus statement for the use of BVS (Chapter 2). We reported that the implantation of a BVS in a *de novo* lesion with a diameter between 2.3 – 2.8 mm and maximum length of 28 mm was indicated as 'Appropriate'. 'Probably appropriate' involved acute coronary syndrome (ACS) patients, long lesions, calcified lesion with proper lesion preparation and provisional bifurcation treatment. Off-label implantation included in-stent restenosis, grafts and vessel with diameter > 4.0 mm. More data needed to be gathered in order create real BVS guidelines.

Part I described the early outcomes of the Absorb BVS using different quantitative techniques. Chapter 3 described the acute angiographic outcomes of BVS when used in a wider range of coronary lesion types such as bifurcation and calcified lesions, chronic total occlusions and long lesions, showing feasible results.

All coronary implant will stretch the natural curvatures in the coronary arteries and reduce the possibility to increase curvatures during cardiac contraction. This alteration in natural morphology does have a known impact on flow patterns and will change shear stress within and at the edges of stents. The longer the lesions and subsequent implants, the more severe the impact will be. In Chapter 4 we compared the conformability of BVS and DES in long lesions (implants of at least 28mm). Due to the difference of materials, the BRS resulted in a non-significant reduction in curvature post-implant while the metallic DES results a significant reduction in curvature of the treated vessel.

Part II reported on the short- and mid-term outcomes of the BVS as investigated in the BVS registries from the Erasmus MC, including a patient population that was more reflective of 'real-world' patients and lesions, such as ACS, bifurcation and calcification.

The BVS Expand registry was the basis for multiple manuscripts, reporting on both angiographic (Chapter 3) and mid-term clinical outcomes (Chapter 5) The BVS Expand registry is an investigator initiated, single-arm, single-centre registry that included patients who presented with non-ST segment elevation myocardial infarction (NSTEMI), unstable angina, stable angina or silent ischemia and who had a *de novo* lesion in vessels with diameter between minimum 2.0 and maximum 3.8 mm by online quantitative coronary analysis (QCA). Main excluding criteria were: previous coronary artery bypass grafting (CABG), presentation with ST elevation myocardial infarction (STEMI) and an expected survival of less than one year. Although advanced age was not an exclusion criterion, BVS were in general reserved for younger patients, and left to operator's interpretation of biological age. We included 249 patients (intention-to-treat population) with mean age of 61.3±10.2 years; 73.5% were male and 18.5% were diabetic. Pre-dilatation was performed in 89.3%, intravascular imaging in 39% and post-dilatation in 53.3%. Device success was 99.2%. Post-procedural reference vessel diameter (RVD) was 2.89±0.42 mm, minimum lumen diameter (MLD) was 2.41±0.41 mm and diameter stenosis (%DS) was 17.6±8.6%. Clinical outcomes at 18 months were acceptable with rate of major adverse cardiac events (MACE) of 6.8% and rate of definite scaffold thrombosis (ScT) of 1.9% (Chapter 5). The BVS STEMI registry was the Erasmus MC's study to investigate the performance of BVS in STEMI patients only. Main exclusion criteria were: known intolerance to contrast medium, uncertain neurological outcome after cardiopulmonary resuscitation, previous PCI with the implantation of a metal stent, left main (LM) disease.

In Chapter 6, using pooled data from both the Expand and STEMI registry, our group described outcomes in ACS patients and non-ACS patients, demonstrating similar one year clinical outcomes. Acute angiographic outcomes such as post-procedural MLD and %DS appeared to be better in the ACS group. But of note, stable patients were older, had more risk factors and often presented with more complex lesions (higher rates of bifurcation, calcification and chronic total occlusions [CTO]). MACE rate and rate of ScT was comparable between groups but the latter represented with a different distribution in time: early ScT (< 30 days) occurred mainly in ACS patients whereas in the stable group, all cases of ScT were clustered between 30 days and 1 year (late ScT).

Our group was the first to describe acute outcomes of the BVS in a small group of STEMI patients, showing excellent expansion, low malapposition and small in-stent protruding masses. [1] Subsequently, we investigated the 18-months clinical outcomes of almost 150 patients, propensity matched with a metallic DES group (Chapter 7). Procedural and angiographic results were similar between groups. However, clinical events rates were higher for the BVS groups. Most events occurred in the first 30 days after implantation and mainly in cases without post-dilatation. This might suggest that the optimisation of the implantation technique in the acute clinical setting is of paramount importance

for optimal short and mid-term outcomes. Performance of the BVS in different lesion subtypes such as bifurcation and calcified lesions was investigated in Chapters 8 and 9. In Chapter 8, 102 patients (107 lesions) with a bifurcation lesion, originating from both BVS Expand and BVS STEMI, were investigated to report performance of BVS in this type of lesion. The focus was on side branch impairment. Patients were included with at least one *de novo* bifurcation lesion involving a side branch ≥ 2.0 mm by visual estimation and treated with at least one BVS. Most patients were treated by T-provisional strategy showing good acute angiographic outcomes. Device and procedural success were 99.1% and 94.3% respectively and side branch impairment during the procedure occurred in 12.1%. One-year results were good with rate of MACE of 5.5% and definite ScT of 2.2%. Chapter 9 studied the effect of calcium on acute procedural and clinical outcomes in patients treated with BVS. Patients with a calcified lesion were older, had more often hypertension and kidney insufficiency and presented less likely with one-vessel disease. Also, the calcified group included more complex lesion types: higher rate of AHA/ ACC type B2/C lesions, bifurcation, total occlusions, longer lesions and with smaller RVD than in the non-calcified group. Device success rate was 99.1% with no significant differences between the groups. The calcified group showed more aggressive lesion preparation and post-dilatation than the non-calcified group. However, acute lumen gain was significantly less in calcified lesions (1.50 ±0.66 mm vs 1.62 ±0.69 mm, p= 0.040) and with lower final MLD (2.28± 0.41 mm vs 2.36±0.43, p=0.046). There were no significant differences in all-cause mortality, definite ScT, TLR and MI between the groups. Late ScT occurred more frequently in the calcified group compared to non-calcified group (2.1% vs 0%, p=0.02).

These results demonstrated that implantation of a BVS in a more complex patient and lesion subset may be feasible and associated with acceptable rate of adverse events. These observations were also reported in other studies.

Chapter 10 described the performance of BVS when investigated by multislice computed tomography (CT) in a BVS Expand sub cohort. Mid-term performance of BVS, when assessed by computed tomography coronary angiogram (CTCA) was good and CTCA as non-invasive investigation was feasible to evaluate scaffold patency and in-scaffold stenosis.

Part III described the implications of failed cases for future applications. Chapter 11 reported pilot imaging observations in 'real-world' patients with BVS thrombosis. Suboptimal implantation with underexpansion, malapposition, and incomplete lesion coverage, often in combination with dual antiplatelet therapy (DAPT) discontinuation appeared to be the major substrate both for acute and late events.

In Chapter 12 both pathophysiology and treatment of BRS failure are discussed. Chapter 13 describes three cases of very late ScT and their possible relationship with DAPT termination before 18 months. In Chapter 14 we report on the impact of DAPT termina-

tion before 18 months on ScT. Data of three Dutch centres were pooled to investigate the impact of DAPT termination on the occurrence of very late ScT. The incidence of ScT was most notable in the first month after DAPT termination.

Chapter 15 was a systematic review and meta-analysis comparing the mid-term (weighted follow-up duration of 30.6 months) clinical outcomes of the BVS with second-generation DES, including seven randomized controlled trials and three observational propensity matched studies. The use of BVS was associated with an increased risk of adverse events (target lesion failure, myocardial infarction, target lesion revascularization and device thrombosis, especially the risk of very late (> 1 year) device thrombosis. However, this did not result in an increased risk of all-cause mortality.

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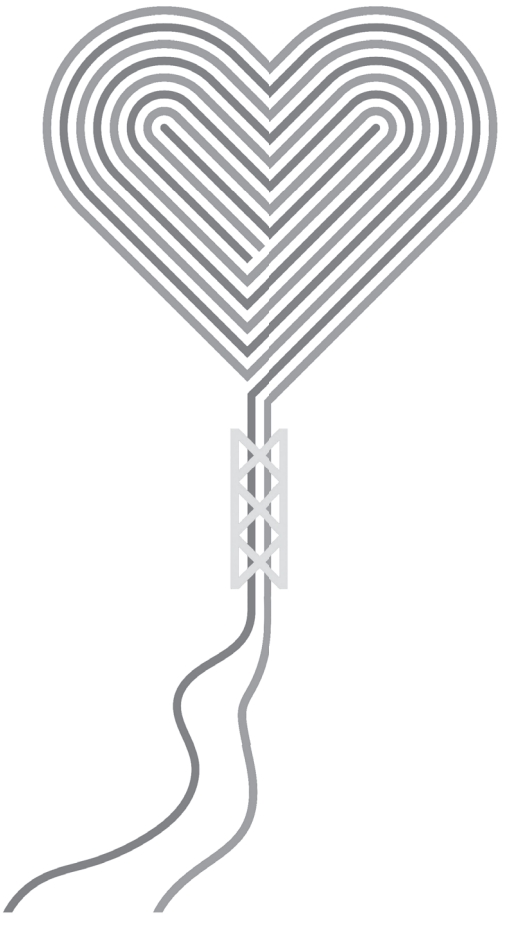
Chapter 17

General Discussion



Percutaneous coronary intervention (PCI) has become an established technique to improve coronary flow when obstructive coronary heart disease results in angina symptoms which cannot be managed with medical therapy or when the myocardium is at risk of necrosis due to acute occlusion. Since the first angioplasty, the field of interventional cardiology has been subject to many developments. The advent of bare metal and drug eluting stents (DES) improved results by reducing the risk of major cardiovascular events. Adverse event rates in the first year post intervention diminished below 10% with convergence approaching 5%. [1] However, contemporary DES are not devoid of limitations such as the risk of stent fracture, coating-polymer induced vascular inflammation and antiproliferative drug related adverse effects. Even the best DES still has an average reintervention rate of 1-2% after the first year. [2] To overcome some limitations of DES, bioresorbable stents (called 'bioresorbable scaffolds' [BRS]) were developed. The concept of a fully bioresorbable scaffold consists of providing only transient support to the vessel with the following hypothesized benefits: improvement of vascular healing after angioplasty with resorption of scaffold material resulting in improved coronary physiology with restoration of coronary flexibility and vasomotion, late lumen enlargement, absence of very late device thrombosis and finally, reduction in target lesion reinterventions in the long-term. The Absorb BVS was the first commercially available BRS, with a poly-L-lactide (PLLA) constitution while eluting everolimus to suppress neointima formation.

Previous research

During the first-in-man (FIM) trials and subsequent strict controlled early registries, BVS was implanted only in highly selected, low-risk patients with low complex lesions. Five-year results of the FIM 'ABSORB Cohort B' were encouraging, revealing late lumen stability and restoration of vasomotor function, together with low event rates. [3, 4] Based on the promising imaging surrogate endpoints of the ABSORB Cohort B, the Absorb BVS received CE mark approval for clinical use in 2011. Superiority testing on angiographic and clinical outcomes for selected patients was hereafter initiated in multiple large randomised clinical trials i.e. ABSORB II, ABSORB III, ABSORB China, ABSORB Japan. However, these studies were not designed to investigate the performance of the BVS in a more complex patient population and hence, these studies will not provide sufficiently data to justify extensive clinical usage beyond the inclusion criteria of the aforementioned trials.

Post-approval registries play an important role in filling the data gap between the performance of a new device in randomized clinical trials (RCTs) and their use in routine practice over time. Furthermore, registries incorporate inherent advantages over clinical trials. Firstly, registries comprise less strict in and exclusion criteria and thus create a more 'real-world' like patient population. Accordingly, results originating from registries are

better generalizable. Secondly, registries provide a longer-term follow-up in comparison to follow-up duration in classic stent RCTs. Thirdly; the larger number of events increases the likelihood of identification of rare events, such as scaffold thrombosis (ScT). Fourth, as registries integrate data of large numbers of (less selected) patients, receiving care in diverse clinical settings, they lead to an enhanced investigation of specific subgroups that are often underrepresented in clinical trials. Furthermore, RCTs usually require a longer preparation time due to a more extensive ethical review process and a requisite appropriate budget where registries frequently provide data earlier in a more general population.

With this in mind, the aim of this thesis is to investigate the clinical safety and efficacy of the first-generation Absorb BVS, when used in routine practice including high risk patients. Furthermore, we attempt to identify potential factors which could influence these outcomes to optimize future patient and lesion selection, procedural strategies and post-procedural pharmaceutical treatment. Lastly, additional information will be collected regarding the mechanisms of scaffold failure in terms of scaffold thrombosis and restenosis to advance this treatment further.

The main observations from this thesis are:

1. BVS used in a routine clinical setting resulted in modest rates of adverse events in the short-term period.
2. Implantation of a BVS in more complex patient and lesion subsets may be feasible and associated with acceptable rate of adverse events.
3. Longer term follow-up and a pooled analysis of complex and non-complex lesions and patients identified an increased risk in adverse outcomes for BVS-treated patients versus current DES.
4. BVS failure was related to procedural techniques, specifically pre- and post-dilatation. Termination of dual antiplatelet therapy (DAPT) before 18 months was another factor which contributed to this failure.

BVS used in the routine clinical setting

The in 2012 initiated BVS Expand and BVS STEMI registries were designed to investigate the performance of BVS in the more complex patient and lesion subsets. The BVS Expand registry included a mixed patient population, involving patients who presented with stable or unstable angina, NSTEMI or silent ischemia. In this registry bifurcation, long lesion, chronic total occlusion and calcified lesions were not excluded. We included 249 patients (intention-to-treat population) with a mean age of 61.3±10.2 years; 73.5% were male and 18.5% were diabetic. Clinical outcomes at 18 months were modest with MACE rate of 6.8% and rate of definite ScT of 1.9%. These results are similar to the largest multi-centre BVS registries such as the GHOST-EU [5], which reported even a slightly

high rate of thrombosis: definite/ probable ScT rate of 2.1% already at six months. The German GABI-R registry showed a MACE incidence of 4.1% after six months and definite/ probable ScT was documented in 1.4% of the patients. [6] More recent registries like IT-DISAPPEARS, showed better results with a device-oriented composite endpoint (DOCE) of 9.9% and a definite/ probable ScT rate of 0.9% at 12 months. [7] In 2018, the RAI registry presented a DOCE rate of 3.9% and a definite/ probable ScT rate of 1.3%. [8]

The BVS STEMI registry was initiated shortly after the BVS Expand registry and recruited exclusively STEMI patients. In theory, ACS patients and particularly STEMI patients would be excellent candidates for implantation with a BVS. They are generally younger and thus have a distinctly longer life expectancy. The plaque burden in their coronary arteries is less extensive and the plaque itself ordinarily consists of soft material, facilitating the embedment of the device into the vessel wall. On the other hand, due to vasoconstriction and the presence of thrombus during the acute setting of STEMI, vessel sizing is challenging with the subsequent risk of undersizing or malapposition. Also, the thicker struts provoke flow disturbances and locally low shear stress, which is an independent predictor of plaque progression. A detailed analysis of the first 31 patients with immediate OCT control (BVS STEMI-first) demonstrated a large vessel lumen with a low percentage of malapposed struts, a small incomplete scaffold apposition area and a small intraluminal defect area. Within 30 day follow-up of the first 49 patients, no scaffold thrombosis occurred. [9]

The full BVS STEMI registry included 151 patients and indicated modest clinical outcomes at 12 months with MACE rate of 8.1% and rate of definite ScT of 2.8%, increasing to 9.8% and 4.3% at 18 months respectively. Event rates were remarkably higher compared to a matched series of DES. When compared to other published literature, for instance the BVS Examination, the same increase of definite ScT versus DES thrombosis was observed although overall lower in both arms (1.7% vs 0.7%). [10] The ISAR-ABSORB MI study, which presented their results during the ESC congress of 2018, with 76.3% of STEMI patients, showed promising results: comparable one-year event rates between the BVS group and the DES group. Definite/ probable ScT rate was 1.7%, the rate of pre-dilatation was 95.3% and finally post-dilatation was performed in 56.6%. [10]

The BVS STEMI registry included STEMI patients only and BVS implantation was performed in an earlier developmental phase than the studies described above, when the operators had less experience, which was reflected by the rates of pre- and post-dilatation (54.1% and 39.7% respectively).

Both registries demonstrated that BVS used in routine clinical setting resulted in modest rates of adverse events with a potential higher risk of the rare event of ScT. The topic ScT needed further investigation in larger data sets and specific analysis of this event and was studied in later sections of this thesis

Implantation of BVS in more complex patient and lesion subsets

Within the combined registries with over 400 patients treated in a single centre, 72% of patients presented with ACS, 29% with bifurcation lesions with side branches >2 mm and 35% with calcified lesions which allowed a more in-depth analysis of these for clinical practice important subgroups.

QCA analysis in the ACS population demonstrated that post-procedural acute lumen gain and percentage diameter stenosis were superior to non-ACS patients 1.62±0.65mm (versus 1.22±0.49mm, P<0.001) and 15.51±8.47% (versus 18.46±9.54%, P=0.04). This did not result in differences in clinical outcomes at one year (MACE of 5.5% for ACS and 5.3% for non-ACS, TLR 3.1% vs 3.2; Def/ Prob ScT 2.4 vs 2.1 %). Noteworthy, ScT outcomes of the most challenging STEMI only population, as reported above, was 2.8% at 12 months rising to 4.3% at 18 months. In this group, the incidence of ScT seems to be most pronounced and warrants further investigation. The high incidence of acute and subacute ScT in this subgroup can be understood from the relationship between the activated coagulation cascade in ACS, the short pre-treatment time within the primary PCI setting and the larger strut thickness and width of the BVS resulting in a larger contact area between blood and stent material. A high incidence of late and very late ScT in STEMI can be elucidated by the relation between stent / scaffold undersizing due to vasoconstriction followed by vasodilatation after successful treatment of the STEMI [11], resulting in a higher rate of strut malapposition compared to stable angina treatment. [12] [13] Malapposition results in larger areas of both abnormal low and high shear stress, resulting in an increased risk of thrombosis and delayed strut coverage with endothelium and neointima. [14]

The use of BVS in patients with bifurcation lesions is also appealing. Permanent metallic stents will always be malapposed along the ostium of the side branch and introduce flow disturbances, assumedly related to the higher post-procedural event rate in bifurcation treatment. More complex stent adjustments with multiple balloons, finalized with kissing balloon post-dilatation, have been advocated to minimize this risk. The potential of full restoration of the natural bifurcation anatomy has been recognized. [15] Contrarily, the relatively broad and thick struts of the BVS could jeopardize the side branch during implantation. When analysing our registries data, we identified 102 patients with 107 bifurcation lesions, having relevant side branches (≥ 2mm in diameter). The incidence of side branch impairment was low (12.1% temporary, 6.5% at end of procedure) with only one failure to rewire and dilate the ostium of the side branch. Two dimensional and three dimensional QCA did not show differences in MLD and % DS in the side branch after treating the main branch with a BVS. In these series, the first-year event rate was acceptable. In larger studies including bifurcations, such as the GHOST-EU[5] and the AIDA RCT[16], treatment of bifurcation lesions was not a predictor of target lesion failure (TLF) or ScT. Our series and the GHOST-EU and AIDA studies, mainly practiced provisional

stenting of the main branch with low numbers of two-stent techniques. Based on these data, provisional scaffolding with BVS can be considered as a favourable treatment option for bifurcations when a meticulous lesion preparation is adhered to. [17]

Calcified lesions constitute a large measure of all coronary lesion types and the treatment of these lesions often result in poorer clinical outcomes. Lesion expansion during balloon angioplasty and the prevention of acute recoil by stent/ scaffold implantation are impaired by dense atherosclerosis. The evaluation of new generation stents in this lesion category is important particularly when ascertaining if the radial force, as measured in bench testing, is clinically sufficient. In smaller series, including 50 OCT measurements post BVS implantation, minimal and mean device area in moderately and heavily calcified lesions were comparable to DES. [18] Only the mean eccentricity index for BVS treated lesions was lower compared to DES, apparently reflecting the slightly lower radial force of BVS compared to contemporary DES. In this thesis, acute lumen gain in calcified lesions, as seen on angiography, treated with BVS was investigated in a much larger subset of 455 patients with 548 lesions. Two hundred of those lesions exhibited at least moderate calcification (angiographically). Despite more aggressive lesion preparation and post-dilation compared to non-calcified lesions, acute lumen gain was significantly less in calcified lesions (1.50±0.66 vs 1.62±0.69mm, p=0.040) with lower final MLD (2.28±0.41 vs 2.36±0.43, p=0.046). No differences in MACE were observed between both groups.

The current thesis revealed that the performance of BVS in the above described lesion subsets may be feasible resulting in acceptable clinical outcomes. Even though ScT may be a more frequent phenomenon in these lesion categories, similar observations have been described in DES platforms. Further investigation concerning the variations in this relatively infrequent phenomenon requires larger studies, meta-analysis of multiple studies and registries or, if available, pooled individual data of prospective RCT's.

Long term follow-up applying pooled analysis of complex and non-complex lesions and patients

Individual one-year results of RCTs (ABSORB II, ABSORB III, ABSORB Japan and ABSORB China), which compared the BVS with its best-in-class counterpart: the second-generation everolimus-eluting stent demonstrated that the BVS was non-inferior to DES. [19-21] Subsequently, the Absorb BVS received FDA approval in July 2016. Remarkably and similar to the European registries, the rate of definite or probable device thrombosis was higher for BVS, although this was not statistically different. [22] Moreover, the first meta-analysis which combined RCT-derived data at one year , performing a patient-level analysis did not show any statistical differences in clinical outcomes at one year. [23] Accordingly, the performance of BVS at one year was deemed promising during the early phase in which solely simple lesions were treated with the device.

To gain further insights in relation to outcomes at one year and beyond in a population that reflects real-world daily practice, both RCTs and registries, inclusive of complex and non-complex lesions, should be incorporated in a meta-analysis. Single arm registries, without a control group, retain a major limitation in practice variability, in particular with respect to patient and lesion selection for a specific procedure. Local propensity matched series avert these concerns and are considered the best alternative when RCT's are not available. We therefore performed a meta-analysis including RCTs and propensity matched registries with a minimum follow-up of 12 months (median follow-up 30.5 months) and including outcomes of 7320 patients. This meta-analysis revealed that BVS was associated with an increased risk of adverse events when compared to DES not only in the first year, but also hereafter. Several other meta-analyses focused on thrombotic events and demonstrated an increased risk of device thrombosis in BVS-treated patients. [24-27] Clearly, the reported increased risk of very late (>1 year) ScT [25, 28, 29] was unexpected. This risk of very late ScT suggests in part an association with the resorption process, which could cause scaffold disintegration with the subsequent risk of thrombosis. [30, 31]

Procedural techniques and the duration of DAPT

Initially, interventional cardiologists implanted scaffolds in an equivalent manner as DES. However, findings in this thesis suggested that the clinical success results after BVS implantation were sensitive to both underexpansion (Chapter 5) and post-dilation (Chapter 7), indicating that a different implantation approach may be indicated for BVS. Similarly, post-hoc analyses from other studies reported that correct scaffold sizing was imperative. Implantation in small vessels (< 2.5mm on visual estimation and < 2.25mm on QCA) increased the rate of DOCE with 60%. [32] Suboptimal implantation of the device was reported to play an important role, both in the short- and long-term, as was illustrated in this thesis in a first careful evaluation of early and late ScT cases. Incomplete lesion coverage, underexpansion and malapposition were revealed as the main potential pathomechanisms for both early and late ScT. This was also observed by a similar study, revealing underexpansion and malapposition as the most frequent determinants of ScT. [31] The sensitivity to underexpansion, implantation in small vessels and malapposition reflexes the difference in stent design, with a larger strut thickness and width causing disruption of laminar flow and inducing large areas with local low shear stress[33]

Based on these observations, a dedicated BVS implantation strategy has been suggested focussing on Pre-dilatation, Sizing and Post-dilatation (PSP) to diminish event rates. [34] However, due to the lack of long-term data and a randomized design that investigates the exact role of an optimal BVS-specific implantation technique, the question remains if optimization of the implantation strategy during index procedure

can legitimately overcome limitations of this device and improve outcomes in the long-term. [35]

Due to increasing evidence of higher rates of very late ScT with an accumulation during the degradation period of the PLLA based device, speculation arose that the optimal duration of DAPT in BVS-treated patients could be at variance compared to the DAPT duration in the DES population. The observations in this thesis, that the rate of ScT immediately after late DAPT termination (minimum of 6 months DAPT) was again increased, suggests that the prolongation of DAPT during the resorption period might be pivotal for BVS. In extension, given the associated risk of bleeding, whether DAPT prolongation is advisable for all patients or for those at higher risk of an event remains uncertain. The supposition of more potent P2Y12 inhibitors administration or a prolonged duration of DAPT with the objective of lowering ScT risk justifies further research with dedicated studies.

Current status of BVS, a first-generation BRS

After the two-year results of the largest RCT (ABSORB III) were presented during the ACC congress in March 2017, the FDA issued a safety alert recommending the use of BVS only in appropriately selected patients, adhering to the updated implantation recommendations and continuation of DAPT for 12 months.[36] Correspondingly, the AIDA trial the two-year results were published earlier than expected after the safety monitoring board recommended to release the preliminary data due to safety concerns. [37] The aforementioned unfavourable findings were again confirmed during the 2017 TCT congress in Denver, USA and in subsequent publications where the three-year data of ABSORB II showed again an increased rate of events in the BVS arm beyond one year. [36] As a consequence, the current generation BVS has been withdrawn from the market. Recently, a Task Force of ESC and EAPCI, justifiably declared that bioresorbable scaffolds should not be preferred above the currently used metallic DES [38].

Concluding, despite the theoretically advantages of the Absorb BVS for the treatment of CAD, this new device appeared to be limited in its application in daily practice as its association with increased risk of adverse events became clear over the foregoing years. Data on the implantation of the device in complex lesions (bifurcations, severely calcified lesions, aorta-ostial lesions and complex CTO lesions) is limited and in general, not in favour of the BVS. Multiple shortcomings exist such as the limitation in overexpansion. Additionally, the thicker and boarder struts importantly contribute to the increased early ScT rate, especially in small vessels or when underexpansion arises. Next generations of BRS need to have a reduction in scaffold struts size, in addition to increased radial strength. Moreover, the resorption time is relatively long, approximately 3 years. The detection of potential beneficial outcome effects would materialise within 3 to 7 years, considering the results of the COMPARE ABSORB and ABSORB III RCTs. Lastly,

in selected patients, the duration of dual antiplatelet therapy could be extended beyond one year and maybe conceivably up to three years, which could be a burden to patients.

Currently, alternative BRS should be reserved only for highly selected patients, used in trials and registries. Notwithstanding BRS implantation in complex lesion subsets such as large vessels (with vessel diameter > 4 mm), small vessels (with vessel diameter < 2.5 mm on visual estimation) should be avoided. One essential deliberation that should requires consideration is that this first-generation device direct comparators enjoy years of experience and subsequent multiple device iterations, has led to lowest event rates currently available. Characteristically, the bar has been set high. Furthermore, the Absorb BVS was used for the first time by most of the operators during the early studies and knowledge concerning an optimal implantation strategy was incomplete in the corresponding period.

It is fair to assume that the era of the first-generation BVS has now been concluded. The ensuing generations of bioresorbable scaffolds will most likely be both fascinating and intriguing when one considers the sage words of George Bernard Shaw "progress is impossible without change, and those who cannot change their minds cannot change anything".

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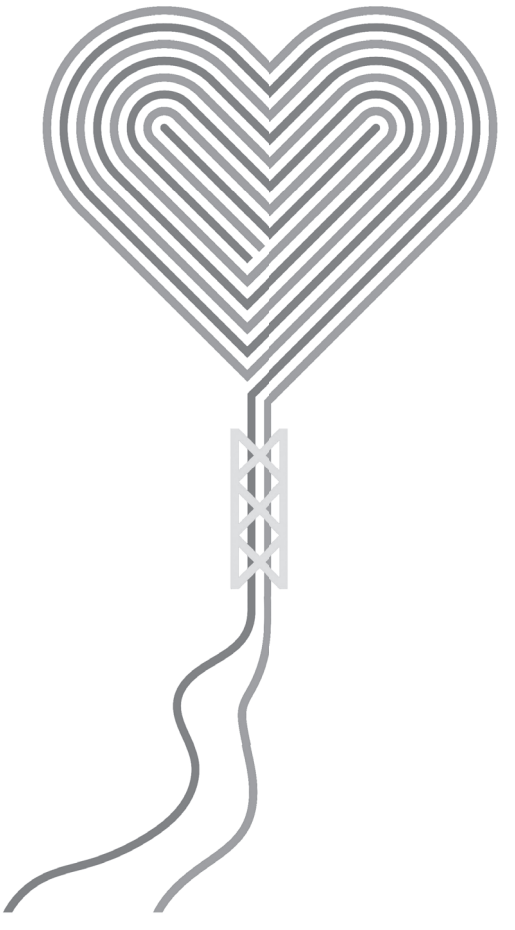

Bij percutane coronaire interventie (PCI) wordt meestal bij voorkeur medicament-afgevende stents (drug-eluting stents [DES]) gebruikt. Er bestaan echter zorgen over het gebruik van DES, dat wil zeggen over neo-atherosclerose, laat-optredende stent-trombose en hypersensitieve reacties op de in de DES voorkomende polymeer. Bioresorbeerbare bloedvatondersteunende stents (BRS), zoals de Absorb Bioresorbable Vascular Scaffold (BVS), zijn een recente innovatie op het gebied van de PCI. Hiermee wordt een concept geïntroduceerd waarbij het natuurlijke genezingsproces na een initiële interventie wordt ondersteund en waarbij geen lichaamsvreemd materiaal achterblijft dat later ongunstige gevolgen kan hebben. Gebruik van de eerste generatie BVS heeft in meerdere studies onder geselecteerde patenten met niet-complexe laesies bemoedigende resultaten opgeleverd, waarbij volledige bioresorptie werd gezien. Dit was aanleiding tot introductie in de reguliere patiëntenzorg. Introductie in de dagelijkse klinische praktijk bij buiten de eerdere geselecteerde patiëntengroepen vallende personen vraagt om een zorgvuldige benadering en voortdurende bewaking van de resultaten. Het doel van dit proefschrift is te onderzoeken hoe veilig en werkzaam de Absorb BVS is bij complexe laesies en patiënten met een hoger risico die worden behandeld in de gevarieerde klinische praktijk.

In hoofdstuk 1 wordt een overzicht gegeven van de op dat moment (2014/ 2015) beschikbare onderzoeken. Deze lieten, bij geselecteerde patiënten en in de tijd beperkt follow-up, bemoedigende resultaten zien. Samen met een groep vroeg bij het onderzoek betrokken gebruikers werd een Nederlandse consensus opgesteld voor het gebruik van de BVS (hoofdstuk 2). Vastgesteld kon worden dat de implantatie van een BVS in een nieuwe laesie met een diameter tussen 2,3 - 2,8mm en met een maximale lengte van 28mm als 'passend' kon worden beschouwd. De ingreep is 'waarschijnlijk passend' voor patenten met een acuut coronair syndroom (ACS), lange laesies, op de juiste wijze voorbereide gecalcificeerde laesies en voor bifurcatiebehandelingen door middel van eenstenttechniek met provisionele zijtak stenting. Tot de afwijkende toepassingen behoren in-stent restenose, stents in grafts en bloedvaten met een diameter > 4,0mm. Om deugdelijke richtlijnen voor het gebruik van BVS te kunnen opstellen is het noodzakelijk om meer informatie te verzamelen.

In deel I worden vroegere resultaten van de Absorb BVS beschreven met behulp van verschillende kwantitatieve technieken.

In hoofdstuk 3 worden de acute angiografische resultaten de BVS beschreven als deze wordt gebruikt bij een breder scala aan coronaire laesies zoals bifurcaties en gecalcificeerde laesies, chronische totale afsluitingen en lange laesies, waarbij redelijke resultaten zijn geboekt.

Coronaire implantaten veranderen altijd iets aan in de natuurlijke kromming van de coronaire bloedvaten en ze reduceren de mogelijkheid die deze krommingen hebben om uit te zetten tijdens de contractie van het hart. Het is bekend dat deze verandering

in de natuurlijke morfologie invloed uitoefent op stromingspatronen en de afschuifspanning binnen en aan de uiteinden van de stents wijzigt. Hoe langer de laesies en dus de implantaten zijn, hoe groter de invloed hiervan zal zijn. In hoofdstuk 4 wordt vergeleken hoe de BVS en DES stents zich aanpasten in het geval van gebruik in lange laesies (implantaten van ten minste 28mm lang). In de context van het gebruik van verschillende materialen gaf de BRS een niet-significante verandering in de bochten na implantatie te zien, terwijl de metalen DES een significante reductie van de bochten van het behandelde bloedvat veroorzaakte.

In deel II wordt gerapporteerd over met de BVS behaalde korte- en middellange termijnresultaten na onderzoek in het BVS-register van het Erasmus MC, dat betrekking heeft op een patiëntenpopulatie die meer overeenkomsten vertoond met 'echte' patienten en waarin laesies zoals ACS (Acuut Coronair Syndroom), bifurcaties en calcificaties voorkomen.

Het BVS Expand-register was de basis voor meerdere tekstverslagen met betrekking tot zowel angiografische (hoofdstuk 3) als klinische resultaten op de middellange termijn (hoofdstuk 5).

Het BVS Expand-register is een door onderzoekers opgezet enkelgroeps, monocentrisch register waarin patiënten zijn opgenomen die zich hebben gepresenteerd met een niet-ST verhoogd myocard infarct (NSTEMI), onstabiele angina, stabiele angina of stille ischemie en bij wie dankzij online kwantitatieve coronaire analyse (QCA) een de novo laesie in een bloedvat met een diameter tussen minimaal 2,0 en maximaal 3,8 mm werd gevonden. De belangrijkste uitsluitingscriteria waren: eerder uitgevoerde coronaire omleidingen (CABG), presentatie met een ST-Elevatie Myocard Infarct (STEMI) en een verwachte overlevingskans van minder dan één jaar. Een gevorderde leeftijd was geen uitsluitingscriterium, maar de BVS werden over het algemeen voorbehouden aan jongere patiënten, waarbij inschatting van de biologische leeftijd aan de betrokken behandelaar werd overgelaten. De groep bestond uit 249 patiënten (die voor behandeling in aanmerking kwamen) met een gemiddelde leeftijd van 61,3±10,2 jaar; 73,5% was man en 18,5% leed aan diabetes. Er was sprake van pre-dilatatie in 89,3%, van intravasculaire beeldvorming in 39% en van post-dilatatie in 53,3% van de gevallen. Het percentage correcte plaatsingen was 99,2%. De postoperatieve referentievatdiameter (RVD) was 2,89±0,42 mm, de minimale lumendiameter (MLD) was 2,41±0,41 mm en de stenosediameter (%DS) was 17,6±8,6%. De klinische uitkomsten na 18 maanden waren acceptabel en lieten een frequentie van grote vasculaire gebeurtenissen (MACE) van 6,8% en een voorkomen van gedefinieerde stenttrombose (ScT) van 1,9% zien (hoofdstuk 5). Het BVS STEMI-register vormde de neerslag van onderzoek aan het Erasmus MC dat uitsluitend de prestaties van de BVS bij patiënten met STEMI betrof. De belangrijkste uitsluitingscriteria waren: bekend met intolerantie voor contrastmedia, onzekere neu-

rologische resultaten na reanimatie, eerder uitgevoerde interventie met een metalen stent, LM hoofdstam laesie (LM).

In hoofdstuk 6 zijn gegevens uit zowel het Expand- als het STEMI-register gebruikt om over de eenjaars resultaten te schrijven van ACS-patiënten en van stabiele patiënten. In de ACS-groep leek minder sprake te zijn van acute angiografische verschijnselen als postoperatieve MLD en %DS. De stabiele patiënten waren echter ouder, hadden met meer risicofactoren te maken en vaak presenteerden zij zich met complexere laesies (vaker voorkomende bifurcaties, calcificaties en chronische totale occlusies (CTO)). MACE en ScT kwamen in beide groepen in vergelijkbare mate voor, maar ScT presenteerde zich op een andere manier in de tijd: vroeg optredende ScT (< 30 dagen) kwam vooral voor bij patiënten met ACS terwijl in de stabiele groep alle gevallen van ScT voorkwamen tussen de 30 dagen en één jaar (laat optredende ScT).

Onze groep was de eerste die de acute uitkomsten van de BVS in een kleine populatie STEMI patienten beschreef met onder andere een goede stent expansie, en weinig malappositie. [1] In hoofdstuk 7 worden de klinische resultaten van STEMI-patiënten over 18 maanden beschreven, afgezet tegen patiënten die met DES waren behandeld in een 1:1 verhouding, waarbij gebruik is gemaakt van de gelijkheidsbenaderingsmethode (propensity matched methode). De procedurele en angiografische resultaten van de twee groepen waren vergelijkbaar. Bij de BVS-groepen kwamen echter vaker klinische gebeurtenissen voor. De meeste van deze gebeurtenissen deden zich voor in de eerste 30 dagen na implantatie en vooral in gevallen waarbij geen postdilatatie had plaatsgevonden. Dit kan erop wijzen dat de optimalisatie van de implantatietechniek in de acute klinische setting van het allergrootste belang is voor optimale resultaten op korte en middellange termijn.

De prestaties van de BVS in verschillende typen laesies, zoals bifurcatie en gecalcificeerde laesies, werden onderzocht in hoofdstuk 8 en hoofdstuk 9. In hoofdstuk 8 wordt beschreven hoe 102 patiënten (107 laesies) met een bifurcatie-laesie, geselecteerd uit zowel het BVS Expand- als het BVS STEMI-register, zijn onderzocht om de prestaties van de BVS bij dit type laesie te kunnen rapporteren. De focus lag op afsluiting van zijtakken. Patiënten in deze groep hadden ten minste één de novo bifurcatie-laesie met een zijtak van ≥ 2,0mm volgens visuele schattingen en waren behandeld met minstens één BVS. De meeste patiënten waren behandeld volgens de 'T-provisional'- strategie en presenteerden zich met goede acute angiografische uitkomsten. De BVS en de procedure waren in respectievelijk 99,1% en 94,3% van de gevallen succesvol; zijtakobstructie gedurende de procedure trad op bij 12,1%. De resultaten na een jaar waren goed: MACE kwam in 5,5% en ScT in 2,2% van de gevallen voor.

In hoofdstuk 9 worden de acute angiografische en klinische uitkomsten van patiënten met een gecalcificeerde laesie (gedetermineerd als een matige of ernstige gecalcificeerde laesie tijdens visuele beoordeling op angiografie) versus patiënten zonder een

gecalcificeerde laesie beschreven. In totaal ging het om 548 laesies. De uitgangspositie van patiënten was verschillend in termen van leeftijd, hypertensie, nierinsufficiëntie en meervoudige vaatziekten (langer bestaand en vaker aanwezig bij patiënten met gecalcificeerde laesies). Patiënten met gecalcificeerde laesies hadden ook vaker complexe laesies: zij lieten meer AHA/ ACC type B2/C laesies, bifurcaties, totaalocclusies en langere laesies met kleinere bloedvatdiameters (RVD) zien dan de niet-gecalcificeerde groep. Onder patiënten met gecalcificeerde laesies werden agressieve laesie voorbehandeling, na-dilatatie en de intra-coronaire beeldvorming vaker toegepast. Het percentage correcte plaatsingen was 99,1% (vergelijkbaar tussen beide groepen). De acute toename in lumen diameter was echter minder in de groep patienten met een gecalcificeerde laesie (1,50 ±0,66 mm versus 1,62 ±0,69 mm, p= 0.04). De uiteindelijke MLD was ook kleiner: 2,28± 0,41 mm versus 2,36±0,43, p=0,046. De klinische resultaten van de groepen waren vergelijkbaar. De ScT presenteerde zich echter op een andere manier in de tijd: bij patiënten zonder gecalcificeerde laesies (meer ACS-patiënten) kwamen de waargenomen gevallen van ScT voornamelijk vroeg voor, terwijl bij patiënten met gecalcificeerde laesies meer late ScT optrad. Dit kan een gevolg zijn van de heterogeniteit tussen de groepen, omdat er een hoger aantal ACS-patiënten in de groep patiënten zonder gecalcificeerde laesies zat, wat een enigszins ander mechanisme voor de ontwikkeling van ScT met zich meebracht.

Bovenstaande hoofdstukken demonstreerden dat de implantatie van een BVS in een meer complexe patienten- en laesiepopulatie bemoedigende resultaten liet zien en geassocieerd waren met acceptabel percentage ongunstige gevolgen.

Hoofdstuk 10 gaat over de prestaties van de BVS tijdens onderzoek door middel van computertomografie (CT) in een BVS Expand-subgroep. De prestaties van de BVS op middellange termijn zijn onderzocht door middel van een computertomografisch coronairangiogram (CTCA) en als 'goed' beoordeeld. CTCA, een niet-invasieve onderzoeksmethode, werd als bruikbaar voor de beoordeling van scaffolddoorgankelijkheid en in-scaffoldstenose beoordeeld.

In deel III worden ten behoeve van toekomstig gebruik, de implicaties van mislukte toepassingen besproken. Hoofdstuk 11 beschrijft beeldvormingsobservaties van een proefproject met 'echte' patiënten met BVS-trombose. Suboptimale implantaties met onvoldoende geëxpandeerde, verkeerd geplaatste implantaten en incomplete afdekking van de laesie, vaak in combinatie met stopzetting van de dubbele anti-bloedplaatjes therapie (DAPT), bleken de belangrijkste voedingsbodems voor zowel acute als later optredende gebeurtenissen te zijn.

In hoofdstuk 12 worden de pathofysiologie en de behandeling van mislukte toepassing van BVS besproken. In hoofdstuk 13 worden drie gevallen beschreven van zeer laat (> 1 jaar) optredende ScT en de mogelijke relatie daarvan met het binnen 18 maanden stopzetten van de DAPT. Hoofdstuk 14 is een verslag van de effecten op ScT van het bin-

nen 18 maanden stopzetten van de DAPT. Om de effecten van het stopzetten van DAPT op het optreden van zeer laat optredende ScT te onderzoeken werden de gegevens van drie Nederlandse centra samengevoegd. De incidentie van ScT was het opvallendst in de eerste maand na de beëindiging van de DAPT.

Hoofdstuk 15 is een systematisch review en meta-analyse waarin de (bij een gewogen-gemiddelde follow-uplooptijd van 30,6 maanden) klinische resultaten van de BVS op de middellange termijn worden afgezet tegen die van tweede generatie DES, inclusief zeven gerandomiseerde gecontroleerde studies en drie observationele studies volgens de gelijkheidsbenaderingsmethode. Het gebruik van BVS wordt geassocieerd met een verhoogd risico op ongunstige gevolgen (falen van de doelwitlaesie [TLF], myocardinfarct [MI], herbehandeling van de laesie [TLR] en stenttrombose [DT]), met name het risico van zeer laat optredende stenttrombose. Dit resulteert echter niet in een verhoogd risico op mortaliteit in het algemeen.

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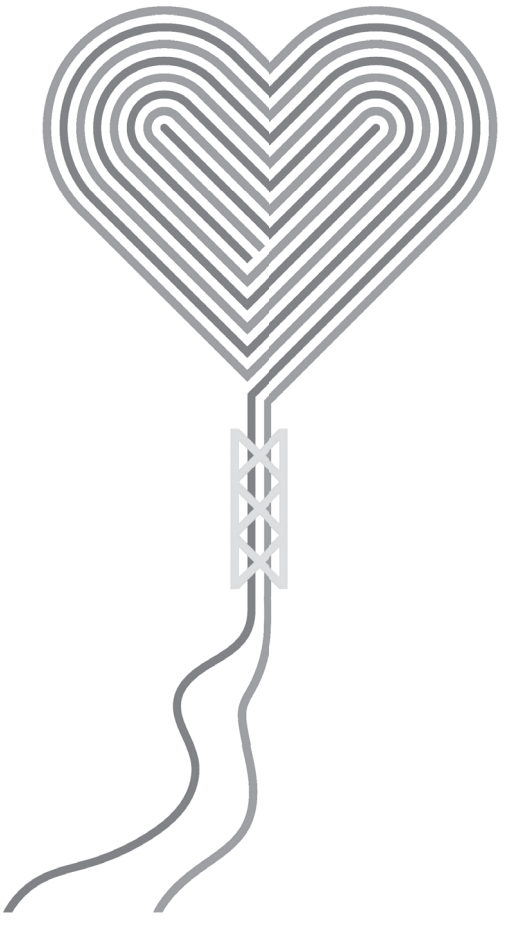
List of publications



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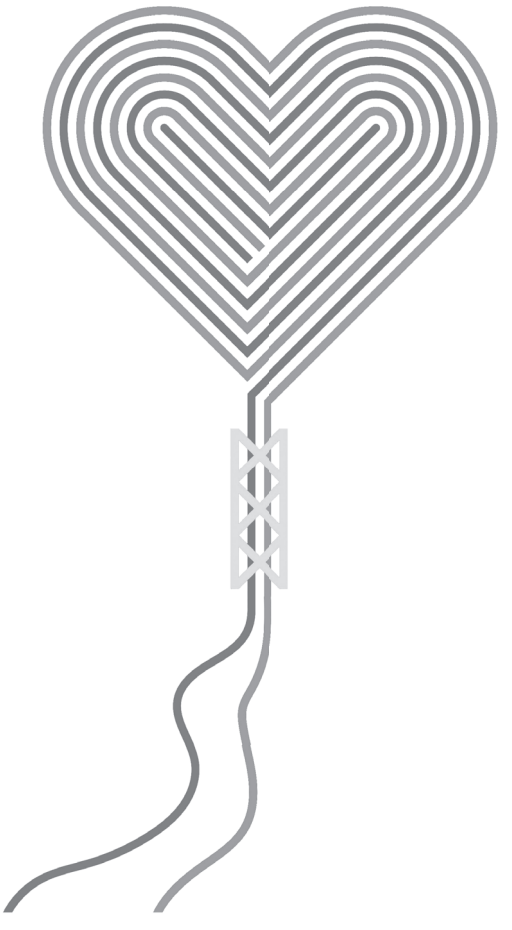
PhD Portfolio

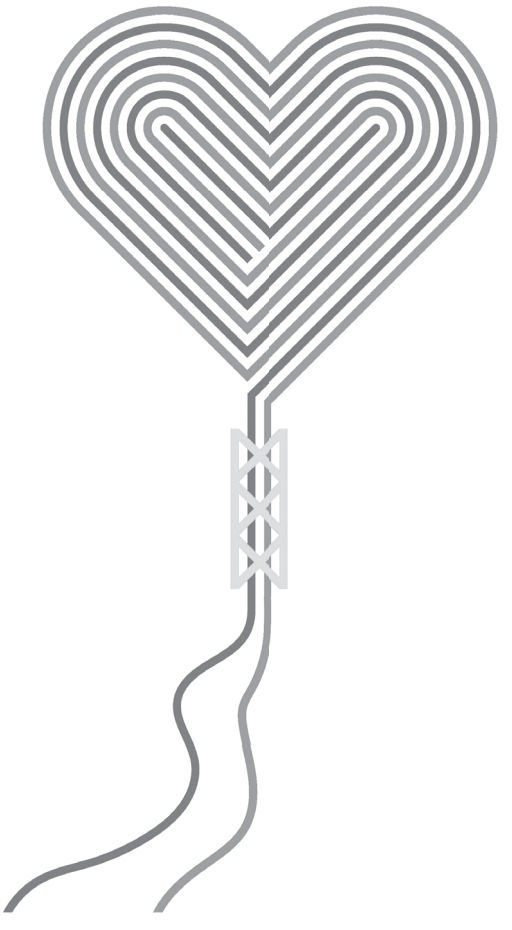


PhD portfolio		
1.PhD training		
	Year	**Workload (ECTS)**
Research skills		
-Openclinica course	2014	
-Systematic literature retrieval course	2015	
-Endnote course	2015	
-BROK course	2014	1.5
-CPO course	2014	0.3
-Biostatistical methods I: Basic Principles	2015	5.7
-NIHES winterprogram	2015	
- Biostatistics for Clinicians		1.4
- Survival Analysis		1.4
- Logistic Regression		1.4
In-dept courses		
-COEUR Arrhythmia Research Methodology	2014	1.5
-COEUR Pathophysiology of Ischemic Heart Disease	2014	1.5
-COEUR Vascular Clinical Epidemiology	2014	1.5
-COEUR Cardiovascular Imaging and Diagnostics	2014	1.5
-COEUR Congenital Heart Disease	2017	1.0
-COEUR Intensive Care	2017	1.0
Conferences		
-NVVC congress 2015, Noordwijk, the Netherlands	2015	1.0
-EuroPCR congress 2015, Paris, France	2015	1.5
-ESC congress 2015, London, United Kingdom	2015	1.5
-TCT congress 2016, Orlando, United States	2016	1.5
-CRT congress 2017, Washington, United States	2017	1.5
-ESC congress 2017, Barcelona, Spain	2017	1.5
Research seminars and lectures		
-COEUR Non-invasive Imaging of Myocardial Ischemia	2014	0.4
-COEUR Structural and Fluid Dynamics in Bifurcated Coronary Arteries	2014	0.1
-COEUR Simulation Tailored Interventional Treatment: Dream or Reality	2014	0.1
-COEUR SALT	2014	0.4
-COEUR Imaging of Cardiac Arrhythmias	2014	0.2
-COEUR Arterial Thrombosis in Acute Ischemic Stroke	2014	0.2
-COEUR Personalized Medicine	2014	0.2
-COEUR Discoveries in Atrial Fibrillation Pathophysiology: Implications for AF Therapy	2017	0.4

2.Teaching activities		
Supervising students		
-2nd year medical student: writing a systematic review	2014	0.5
-2nd year medical student: writing a systematic review	2016	0.5

Presentations		
-NVVC congress 2015, Noordwijk, the Netherlands	2015	0.3
-EuroPCR congress 2015, Paris, France	2015	0.3
-ESC congress 2015, London, United Kingdom	2015	0.3
-CRT congress 2017, Washington, United States	2017	0.3
-ESC congress 2017, Barcelona, Spain	2017	0.3

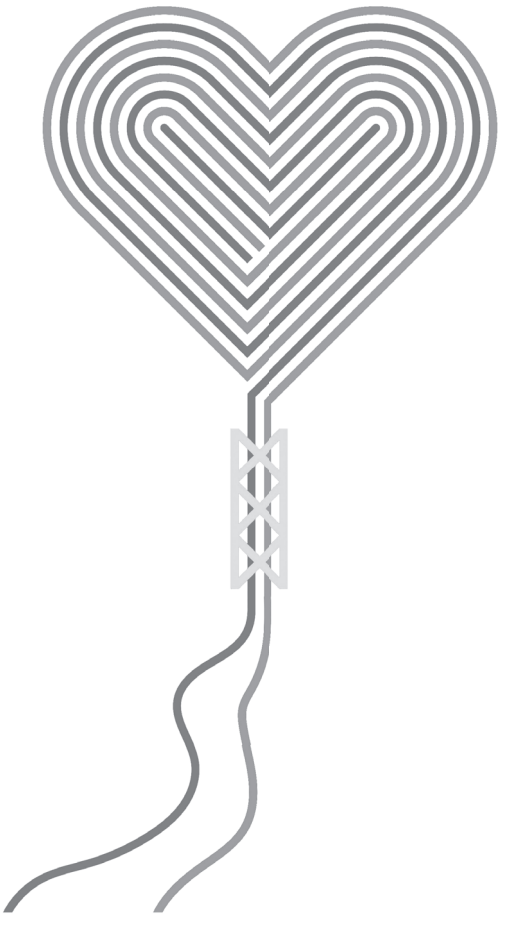
About the author



Cordula Marie Felix was born on June 16th 1988, in Rotterdam, the Netherlands. After finishing secondary school (Erasmiaans Gymnasium Rotterdam) in 2006, she started medical school at the Erasmus Medical Centre (EMC) in Rotterdam. During her study, she spent two research internships abroad (San Francisco, USA and Windhoek, Namibia) and was part of the organizing committee of the IFMSA Teddy Bear Hospital. The two main clinical internships were in the Internal Medicine department and Emergency Room. In December 2012, she obtained the degree of medical doctor at the EMC in Rotterdam. Hereafter, she started working as a resident (ANIOS) at the department of Internal Medicine in Maasstad Hospital, Rotterdam. In December 2013, she initiated her PhD at the cardiology department of the Erasmus Medical Centre under supervision of prof. dr. R.J.M. van Geuns. During her PhD project, she investigated the performance of the Absorb bioresorbable vascular scaffold (BVS) for the treatment of coronary artery disease when used in daily practice.

As of March 2018, Cordula is working as a GP in training in Zandvoort. Besides work, she enjoys her family (partner Victor van den Berg and three children Oscar, Pepijn and Hannah), her friends and sports.

Dankwoord/ Acknowledgements



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